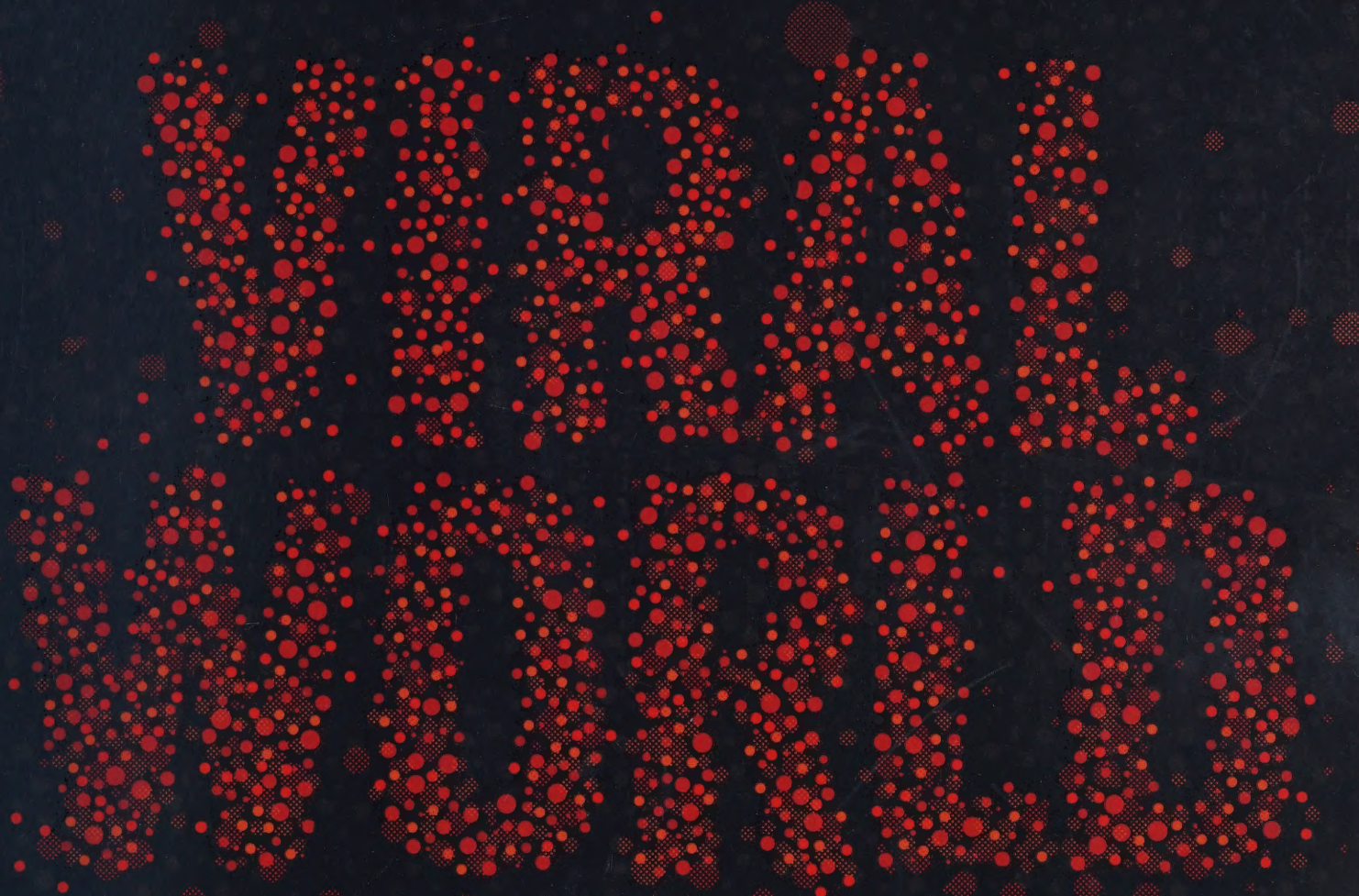
HARVARD medicine

SPRING 2022



Scientists unravel the astonishing roles viruses have in our lives and in life on Earth



a sense of place

SPRING APPAREL: The HMS Quad is a year-round canvas for nature's seasonal expression. But it may be Spring that brings out its best. The changes do not happen all at once, but instead unfold, ushered in by the right mixture of temperature, sunlight, and rain. Early signs of the season include robins hopping across the greening lawn. These winged scouts are soon joined by what many consider the main event: the flowering of the trees. This gnarled beauty stands in a small grassy square between imposing buildings. Its blooms will soften the edges of the buildings and the view for winter-weary eyes.

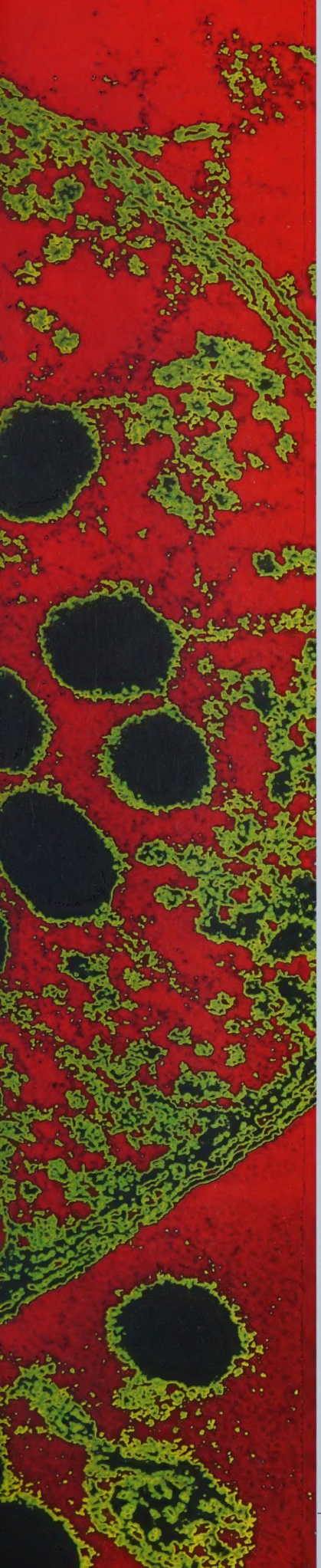


STEVE LIPOFSKY



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TINY INSIGHTS: The black ovals in this color-enhanced transmission electron micrograph are T2 bacteriophages that have infected an *Escherichia coli* bacterium. In laboratory experiments conducted in the early 1950s, the T2 bacteriophage was used to show that only the phage's nucleic acids were required for its replication, a finding that ultimately helped support the theory that DNA is genetic material.



MATTIAS PALUDI (COVER); LEE D. SIMON/SCIENCE SOURCE

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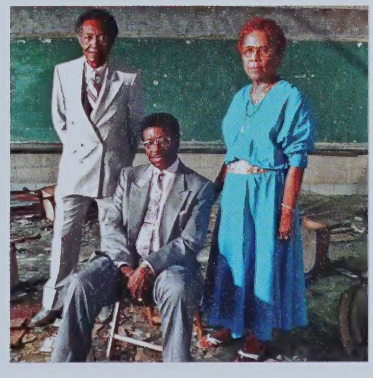
Alumni recall their favorite places to study while students at HMS



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The Power of Collaboration



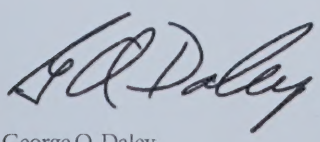
THROUGHOUT THIS CONTINUING PANDEMIC, I have highlighted the work of MassCPR, the Massachusetts Consortium on Pathogen Readiness. This regional and transnational effort has brought the expertise of hundreds of scientists, clinicians, and public health experts to confront a virus that threatens all people. Their ability—and willingness—to act together against SARS-CoV-2 has helped mitigate the more serious consequences of COVID-19 and offered us the chance to return to some semblance of normalcy. The consortium's continuing work to better anticipate emerging pathogens will help protect us against global health threats for years to come.

The role that HMS researchers have taken in the global endeavor to fight back against this deadly virus fills me with pride. One alumnus, Dan Barouch, MD '99, the William Bosworth Castle Professor of Medicine, professor of immunology at HMS, and director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center, worked tirelessly on the development of what became the Johnson & Johnson/Janssen COVID-19 vaccine, one of three vaccines authorized by the U.S. FDA. Richard Sidman, MD '53, the HMS Bullard Professor of Neuropathology, Emeritus, was part of a team of researchers that showed that bacteriophages—viruses that infect bacteria—could potentially be used to deliver COVID-19 vaccines, while Connie Cepko, the Bullard Professor of Genetics and Neuroscience in the Blavatnik Institute at HMS, used viruses to develop a rapid-test tool for SARS-CoV-2.

Many of our researchers are focused on understanding the complexities of SARS-CoV-2, just as many others are concentrating on uncovering how viruses can be used to prevent disease or even to heal. For example, in 2019, a team led by Georg Gerber, MD '09, an HMS associate professor of pathology at Brigham and Women's Hospital, and Pamela Silver, the Elliot T. and Onie H. Adams Professor of Biochemistry and Systems Biology at HMS, reported that when phages in the human gastrointestinal tract kill specific bacteria, the action causes metabolic fluctuations throughout the body, even extending to neurotransmitters. Their findings could inform work on using phages as therapeutics to manage conditions such as depression.

Another collaborative research effort has produced an adeno-associated virus (AAV) that delivers gene therapy directly to muscle tissue, a potential breakthrough treatment for genetic muscle diseases. The research, which involved Pardis Sabeti, MD '06, a professor of organismic and evolutionary biology and of immunology and infectious diseases at Harvard and a member of the Broad Institute of MIT and Harvard; Amy Wagers, the Forst Family Professor of Stem Cell and Regenerative Biology at Harvard and HMS; and Sharif Tabebordbar, PhD '16, a former member of Sabeti's lab who co-founded and now serves as chief scientific officer of a California-based therapeutics start-up, is serving as the basis for the development of a new AAV-based gene therapy.

These collaborations and discoveries exemplify the intense intellectual pursuit of scientific knowledge that is so deeply woven into the DNA of HMS researchers. Our scientists' investigations of the intricacies of entities as fundamental as viruses is but one way in which they strive to enrich the body of scientific knowledge and pave the way to better health for people throughout the world.



George Q. Daley
Dean of Harvard Medical School

RANDY GLASS

HARVARD medicine

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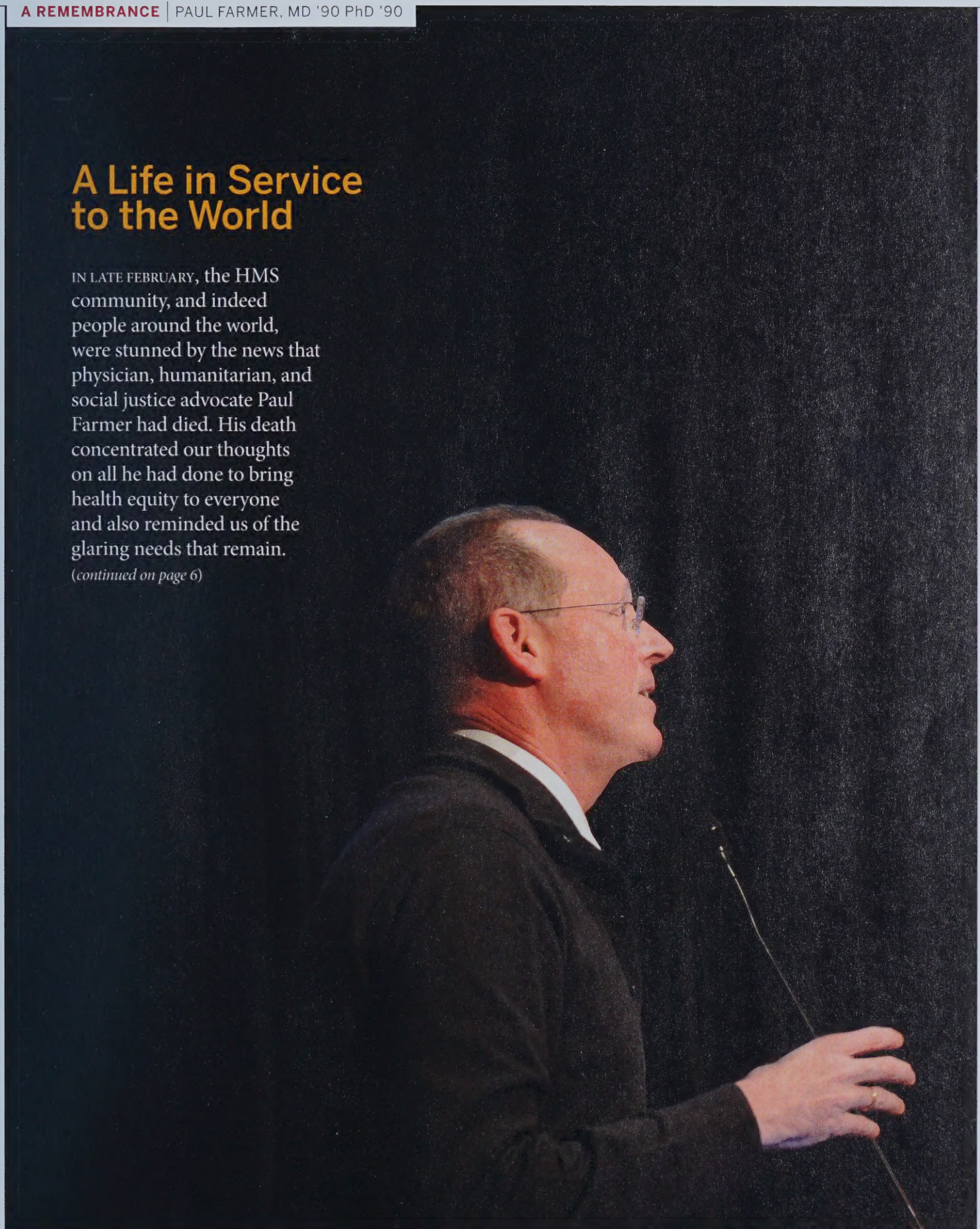
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A Life in Service to the World

IN LATE FEBRUARY, the HMS community, and indeed people around the world, were stunned by the news that physician, humanitarian, and social justice advocate Paul Farmer had died. His death concentrated our thoughts on all he had done to bring health equity to everyone and also reminded us of the glaring needs that remain.

(*continued on page 6*)



RICK GROLEAU



A March candlelight vigil on the Quad commemorated the life and contributions of Paul Farmer, Kolokotrones University Professor and chair of the Department of Global Health and Social Medicine in the Blavatnik Institute at HMS, chief of the Division of Global Health Equity at Brigham and Women's Hospital, and co-founder of the humanitarian nonprofit Partners In Health.

STEVE LIPOFSKY; JOLYGON/ISTOCK/GETTY IMAGES (FACING PAGE)

The HMS community drew together to commemorate the person who had led a dynamic Quad department, co-founded a global health and social justice nonprofit, lectured and written widely on the importance of health care as a human right, taught medical and graduate students throughout the world, and mentored and inspired scores of individuals at HMS and elsewhere.

Of the several ceremonies celebrating Farmer and his life, a candlelight vigil on the Quad may have epitomized the solidarity that Farmer nourished and inspired within the HMS community. Although the early March evening was cold, there was an abiding warmth in the words shared. Among the speakers was George Q. Daley, MD '91, dean of Harvard Medical School. The following comes from remarks he made on that evening and in other communications to the HMS community.

I was heartbroken by the news that Paul Farmer had died in Rwanda. He was working and teaching at the University of Global Health Equity, an institution he co-founded. As devastated as I was, I knew that it was poignant, even poetic for Paul to breathe his last in a place that reflected his unceasing effort to bring exceptional medical care to people in great need of such care throughout the world.

Paul was a great teacher. And it was my extraordinary privilege to learn from him, to learn about the process of building health equity, about how to fight for the health and dignity of the most vulnerable patients, and about what it means to commit yourself to providing the most expert and compassionate of care to everyone.

Paul was not just one in a million, not just one in a generation. Paul was arguably singular in history, for he made history. He was a compassionate physician and infectious disease specialist, a brilliant and influential medical anthropologist, and among the greatest humanitarians of our time. He dedicated his life to improving human health and advocating for health equity and social justice on a global scale. He expressed conviction to this idea in many ways and at many times, but one statement stands out for me in particular:

"The essence of global health equity is the idea that something so precious as health might be viewed as a right."

It's a simple statement, but, as was often true for Paul, it also is radical, inspirational, and unambiguous.

Paul was, at his core, and to the very end, a doctor, and his presence brought great honor to Harvard Medical School. His example will always be a reminder that a doctor's truest calling is to care for the sick and ailing. His life's work and teaching have been an inspiration to countless colleagues and trainees who will continue to carry on his legacy.

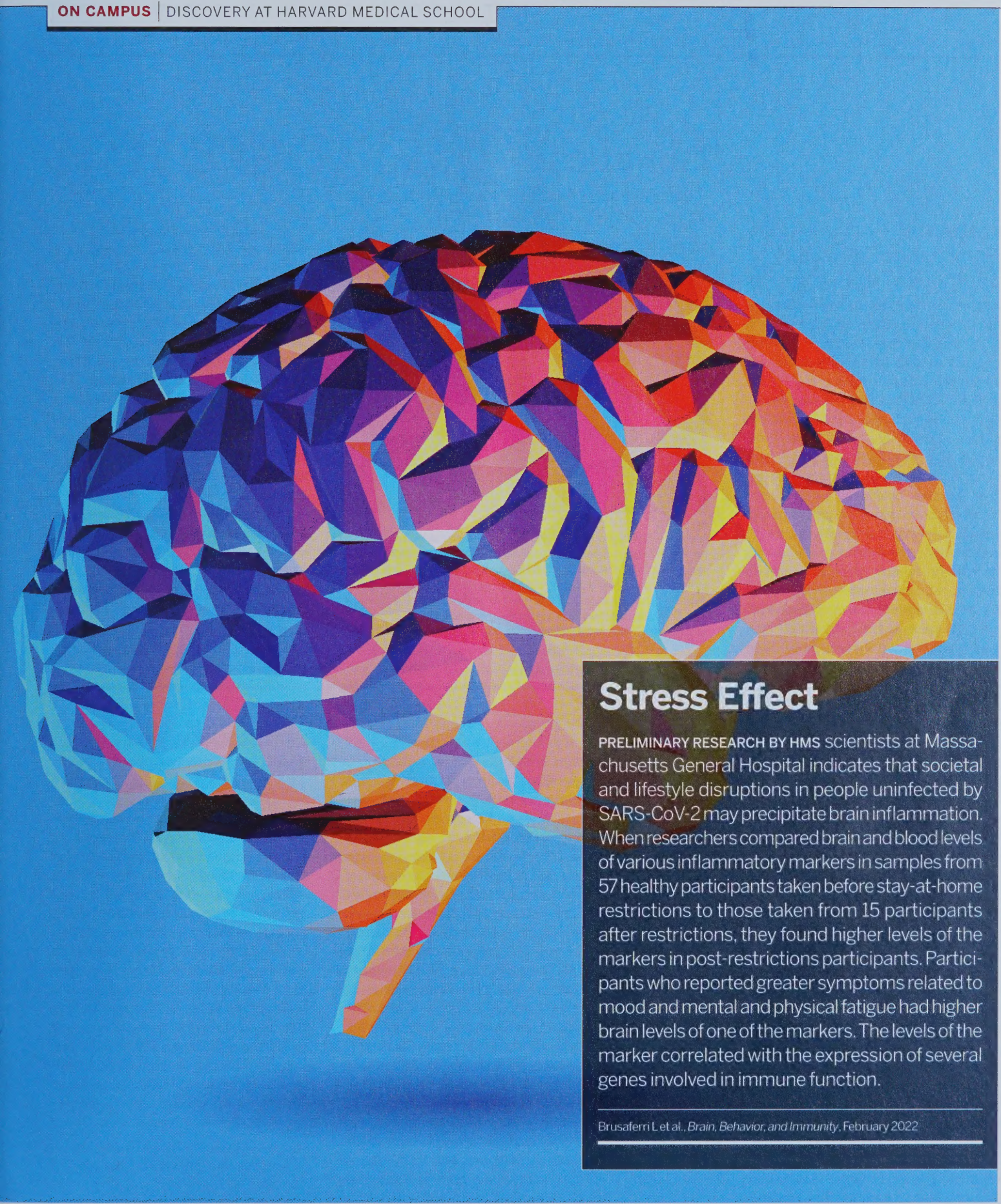
Paul championed the concept of accompaniment. It's the notion of being present on a journey with someone and committing to that person's well-being. Paul espoused the role of accompaniment in delivering complex care to people with life-threatening illnesses in resource-poor settings. He believed that compassion must be permanently and universally embedded in a clinician's work, and that the process of accompaniment—which implies a deeply held sense of the value and dignity of all human life—does not, or need not, undermine scientific rigor, but in fact, enforces it.

We all need to be accompanied sometimes, and this is one of those times. Many of us who knew Paul are hurting, and our community will be healing the deep wound of Paul's tragic passing for quite a while. Yet, we have the opportunity to accompany one another through our pain and to rededicate ourselves to sustaining everything that Paul believed in and stood for.

I will admit that Paul's death shook me deeply, and the unwelcome fact continues to surface unexpectedly during my daily activities. He was not only a consummate colleague and a beloved mentor, but my close friend. To me, he represented the heart and soul of HMS.

It is far from a platitude, however, to say that the people who leave us live on inside of us. Paul was larger than life, and it is important that we preserve his spirit, work, and impact. He was committed to a higher purpose and to being in service to those in greatest need around the world.

I believe that all of us in the HMS community near and far seek to emulate Paul's promise to the world and his commitment to serving the needs of those who face inequitable access to the basic human right of medical care. His commitment to a higher purpose and his embodiment of the HMS mission animated every fiber of his being. We each have a role to play in being diligent stewards of his legacy. I am humbled by the opportunity to do my part to keep his spirit and vision alive.



Stress Effect

PRELIMINARY RESEARCH BY HMS scientists at Massachusetts General Hospital indicates that societal and lifestyle disruptions in people uninfected by SARS-CoV-2 may precipitate brain inflammation. When researchers compared brain and blood levels of various inflammatory markers in samples from 57 healthy participants taken before stay-at-home restrictions to those taken from 15 participants after restrictions, they found higher levels of the markers in post-restrictions participants. Participants who reported greater symptoms related to mood and mental and physical fatigue had higher brain levels of one of the markers. The levels of the marker correlated with the expression of several genes involved in immune function.

Brusaferri L et al., *Brain, Behavior, and Immunity*, February 2022

NEUROBIOLOGY

Early traumas linked to adult neuropsychiatric ills

A RECENT STUDY INVOLVING FORMER National Football League players is adding a new dimension to research investigating whether the trauma resulting from abuse and neglect early in life carries into adulthood.

The study found that although former professional football players experienced childhood adversity at rates similar to the general population, those reporting a childhood history of abuse and neglect were more likely to screen positive for dementia and were placed at significantly greater risk for pain and depression in their later years.

Former NFL players who reported having four or more adverse experiences in childhood were 60 percent more likely to suffer concussion symptoms during their football career, 48 percent more likely to screen positive for dementia, and at greater risk for cognitive problems in later life compared with players who did not report these experiences.

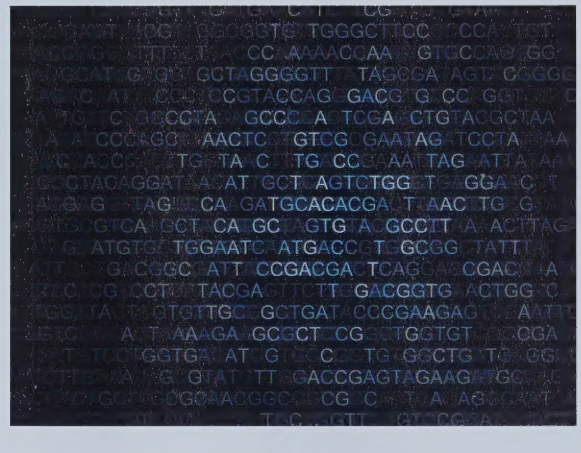
Because instances of childhood adversity were strongly associated with concussion symptoms, the researchers recommend that adverse childhood experiences be investigated in pro football players and other groups as a possible indicator of high concussion risk.

The conclusions are drawn from data gathered for the Football Players Health Study at Harvard University, a study based on surveys of 1,755 former NFL players ages 28 to 92 administered by researchers at HMS and the Harvard T.H.Chan School of Public Health.

Roberts AL et al., *JAMA Network Open*, March 2022

Genetics

Cerebral palsy may be linked to underlying genetic factors in some patients



Although cerebral palsy has widely been viewed as resulting from perinatal oxygen deprivation or another birth-related factor such as prematurity, a study by HMS researchers at Boston Children's Hospital has shown that it may be the result of an underlying genetic condition in up to 25 percent of patients with the disorder. The findings could help doctors make more specific diagnoses and develop more targeted treatment plans for some patients.

Chopra M et al., *Annals of Clinical and Translational Neurology*, January 2022

DIABETES

Enzyme may avert kidney disease in type 1 diabetes

NEARLY TWO MILLION PEOPLE in this country have type 1 diabetes, a disease marked by the body's inability to produce enough insulin to control blood sugar levels. The high blood sugar levels that can result can lead to hyperglycemia and, among other adverse conditions, an increased risk of kidney disease.

In studies involving mouse models, HMS scientists at Joslin Diabetes Center recently shed new light on how hyperglycemia contributes to kidney disease and uncovered a potential therapeutic target. Their work relied on information gleaned from the Medalist study, Joslin's long-running observational study of more than 1,000 people with type 1 diabetes who have successfully managed the disease for 50 years or more. Scientists have found that disease outcomes differ for members of the Medalist cohort compared with other people with type 1 diabetes. For example, as many as 30 percent of people with diabetes experience kidney disease, but just 13 percent of Medalists do.

Prior studies of this cohort showed that individuals who were protected from diabetic kidney disease had higher levels of glucose-metabolizing enzymes than people with diabetes who developed diabetic kidney disease.

To understand the role that one of these enzymes, PKM2, may have in protecting against kidney disease, the researchers used a mouse model genetically engineered to overproduce the enzyme, then compared the kidneys of the engineered mice to those of nonengineered mice with and without induced diabetes. Their findings showed that the overexpression of PKM2 prevented multiple pathological changes to the cells of the kidney's filtration system frequently seen in diabetes, preserved cell function, and prevented disease progression.

The results suggest that blood PKM2 levels could serve as a biomarker for the progression of diabetic kidney disease in patients with diabetes.

Fu J, Shinjo T et al., *Journal of Clinical Investigation*, March 2022

CLINICAL MEDICINE

Delirium severity can be measured using new tool

DELIRIUM IS A SERIOUS CHANGE in brain function that affects up to 64 percent of older medical patients and up to 50 percent of older surgical patients. It can appear as sudden confusion, agitation, memory loss, or hallucinations and delusions and is linked to longer hospital stays and increased risks of dementia and death.

Although more than thirty instruments can identify delirium in patients, few assess its severity. Now, HMS scientists at Beth Israel Deaconess Medical Center and Hebrew SeniorLife have developed a measure of delirium severity that could improve patient-centered care for delirium. The tool, the DEL-S delirium severity score, provides severity measures significantly associated with clinically relevant outcomes.

Vasunilashorn SM et al., *JAMA Network Open*, April 2022

JUSUN/ISTOCK/GETTY IMAGES

noteworthy

Two administrative leaders welcomed to campus

TWO HMS ACADEMIC and administrative offices have changed leadership in the past few months. In September 2021, Kristin Bittinger (*fig. 1*) was appointed dean for faculty and research integrity. Leading the Office for Academic and Research Integrity, Bittinger oversees a coordinated approach to research policy setting, implementation, and compliance, including issues of conflict of interest, research misconduct, student misconduct, and authorship disputes. She works closely with senior colleagues at HMS, the Harvard School of Dental Medicine, and HMS-affiliated hospitals and research institutions and provides advice and consultation to faculty and senior administrators.

Bittinger has more than a decade of service at Harvard, including in her role as HMS chief integrity officer and previously as executive director of external education and director of scientific integrity. She also served as an associate attorney in the Harvard Office of the General Counsel. She succeeds Gretchen Brodnicki.

In January, Julie Joncas joined HMS as chief financial officer. In this role, Joncas leads the Office of Finance, where she is responsible for managing all aspects of the School's annual budget, for ensuring the financial sustainability of HMS, and for helping to advance critical investments in the School's research and education mission. As a strategic partner to senior administrative and department leadership, she provides financial counsel in support of the institutional priorities, infrastructure, and evolving needs of HMS.

Joncas brings to her new role more than 20 years of financial and operational management expertise gained at academic medical institutions in Boston. She served most recently as the system vice-president of finance and CFO for Boston Medical Center.

Joncas succeeds David Smallwood, who had been serving as interim CFO. Smallwood is continuing his service to the School with expanded responsibilities.

A milestone anniversary for social medicine at HMS

THIS PAST YEAR MARKED 150 years of the School's Department of Global Health and Social Medicine (*fig. 2*) helping to "define social medicine as a rigorous field of research and scholarship, as an analytic and teaching toolkit, and as a robust framework for praxis," as described in September 2021 by Paul Farmer, MD '90 PhD '90, Kolokotrones University Professor of Global Health and Social Medicine and chair of the Department of Global Health and Social Medicine in the Blavatnik Institute at HMS, in a reflection published online.

Over the years, the department's name has changed to reflect the growing complexity of social medicine. In 1871, the Department of Hygiene was formed. It was led by founding chair George Derby, MD 1843, a surgeon in the Union Army during the U.S. Civil War and an early leader of the Massachusetts State Board of Health. Later, the department's name changed to Preventive Medicine and Hygiene; then Preventive Medicine; Preventive and Social Medicine; Social Medicine and Health Policy; and Social Medicine. In 2008, it became the Department of Global Health and Social Medicine, led by Farmer.

Bringing intellectual rigor to the mission to improve the well-being of people has been fundamental to the department throughout its existence, noted Scott Podolsky, MD '97, a professor of global health and social medicine and director of the Center for the History of Medicine at the Francis A. Countway Library of Medicine, during a presentation on the department's history.

According to Podolsky, in a paper published in 1870, Derby wrote that the active prevention of disease required a focus on the "conditions in which people live, and the diseases associated with such conditions." Those social conditions, their relationship to illness and health, and the meanings people attach to illness are still a central focus of the department, said Podolsky. It is a focus that inextricably links social conditions with health and well-being.



fig. 1



fig. 2



fig. 3

"The fundamental intuition that what occurs outside the body influences what occurs within it has been a constant throughout the department's evolution," Farmer wrote. "It continues to serve as a powerful rationale for the presence of social medicine at a medical school."

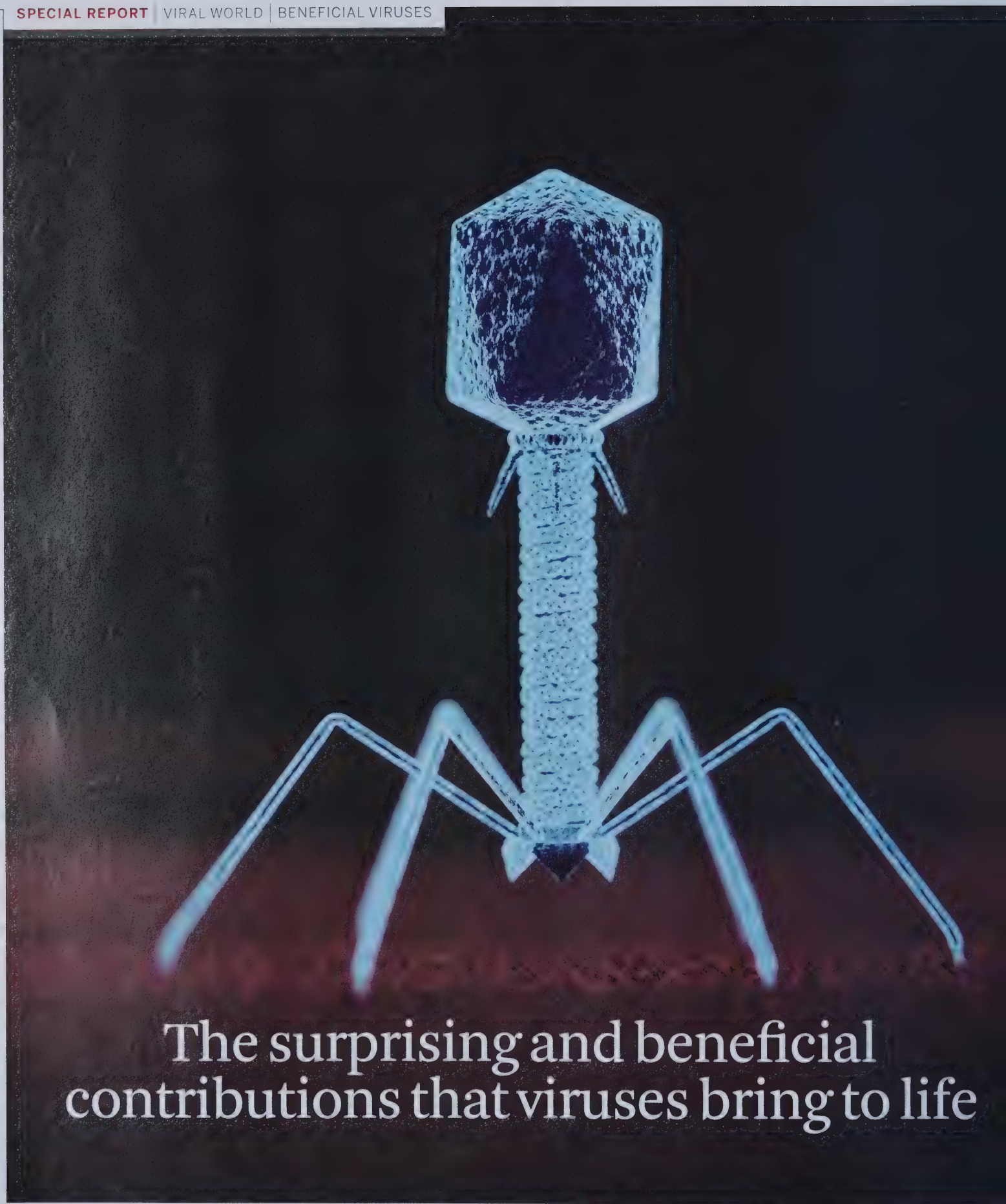
Institute to integrate natural, artificial intelligence

LATE LAST YEAR, the Kempner Institute for the Study of Natural and Artificial Intelligence was launched. A University-wide initiative that spans the Longwood and Cambridge campuses, the institute's leadership will be shared by Bernardo Sabatini, MD '99 PhD '99, the Alice and Rodman W. Moorhead III Professor of Neurobiology in the Blavatnik Institute at HMS (*fig. 3*), and Sham Kakade, the Gordon McKay Professor of Computer Science and Statistics at the Harvard John A. Paulson School of Engineering and Applied Sciences.

Funded by a $500 million gift from the Chan Zuckerberg Initiative, the institute's members will research the fundamental principles that underlie both human and machine intelligence. The fruits of the discoveries are expected to enhance our understanding of how humans think, perceive the world around them, make decisions, and learn, and to advance the rapidly evolving field of artificial intelligence. The institute will also provide funding support to undergraduate and graduate students and postdoctoral fellows and support ten new faculty appointments, significant new computing infrastructure, and resources to allow students to move between labs in pursuit of ideas and knowledge.

In an interview about the role of the new institute, Sabatini said, "The institute is designed to bring together two fields to create something that's essentially new. We also want this institute to be a destination: If you care about intelligence, you should want to come to this institute."

RANDY GLASS



The surprising and beneficial contributions that viruses bring to life

Appearances Deceive

BY STEPHANIE DUTCHEN

Paris, 1917. Hospitalized soldiers were dying from dysentery as *Shigella* bacteria overwhelmed their guts. Nothing could be done for them. Antibiotics wouldn't be discovered for another decade. ■ Experimenting with *Shigella* cultured from the ill, microbiologist Félix d'Hérelle uncovered a difference between samples from patients who survived and those who succumbed. In survivors, an entity too small to be seen through his microscope was killing the bacteria. He called the attackers bacteriophages, or bacteria eaters. ■ D'Hérelle recognized that the mysterious phages offered a way to fight bacterial infections. In 1919, he isolated phages from *Salmonella* bacteria that were causing a typhoid outbreak in chickens and used them to cure the birds. A few months later he thought he would risk treating a boy with a dire case of dysentery. First, however, d'Hérelle and his team drank a concoction of phages they'd isolated from another dysentery patient. When no one felt the worse for wear, they gave it to the boy. ■ He recovered. ■ Advances in microscopy later revealed what phages really are: viruses that infect bacteria and single-celled microbes known as archaea while ignoring plants and animals. ■ Endeavors like d'Hérelle's have helped show humanity that viruses can provide medical and research benefits.



Connie Cepko

#NotAllViruses

Although some two hundred kinds of viruses are known to infect, sicken, or kill us, as the emergence of SARS-CoV-2 has most recently hammered home, that's only one part of the picture. Viruses also keep us alive. They form part of the body's microbiome and safeguard our health. They can be harnessed to treat illness, deliver vaccines, and diagnose infections. They're wielded as research tools to illuminate biology and disease and develop new drugs. We can thank snippets of viral genomes, incorporated into our DNA tens of millions of years ago, for how our reproductive and nervous systems work.

Protovirus components likely even contributed to the emergence of life on Earth, and viruses continue to drive evolution today. They form a crucial part of the global ecosystem that allows us to survive.

"We can't generalize viruses as being harmful," says Mohammadsharif (Sharif) Tabebordbar, PhD '16, who led the development of an experimental gene therapy that uses modified virus components.

"Despite the devastating effects of viral diseases, the viruses that count most in our lives are crucial not in disease but in health and in all aspects of life," says Eugene Koonin, an expert on the genetics of evolution and viruses at the National Institutes of Health's National Center for Biotechnology Information.

While scientists and physicians across the HMS community study ways to combat the viruses that plague us, other colleagues are uncovering and exploiting viruses' potential for good. Some, like Connie Cepko, the Bullard Professor of Genetics and Neuroscience in the Blavatnik Institute at HMS, do both.

"We love viruses for all of our work," says Cepko. Her lab members have devised virus-based tools to map circuits in the brain, prolong vision in mouse models of inherited blindness, and test for SARS-CoV-2.

"Viruses are useful in a ton of ways in research and the clinic," agrees Timothy Lu, MD '10, an associate professor of biological engineering and electrical engineering and computer science at MIT and CEO at Senti Biosciences. "We have these amazing, approved therapies, yet we're just scratching the surface of what viruses can do to modify and treat diseases."

The old is new again

Strangely, the idea of phages as treatments has never overcome initial skepticism. Outside of areas such as eastern Europe, the medical community discarded them when antibiotics emerged mid-century. Today, however, phage-based therapies are gaining traction.

That's partly because phages kill bacteria in a different way from antibiotics, offering a potential lifeline as antibiotic resistance plays a role in the deaths of 5 million people each year worldwide. Phages also offer pinpoint targeting, since most phages evolved to infect one or a few strains of bacteria or archaea. Identifying the bacterium causing a patient's illness and finding a phage that kills it could wipe out the troublemaker and leave beneficial bacteria unharmed.

In the past few years, doctors operating under compassionate use allowances have saved a small number of people from life-

threatening bacterial infections that defied all other treatments. The number of phage therapy clinical trials is ticking upward. In 2021, the U.S. FDA and the National Institute of Allergy and Infectious Diseases awarded $2.5 million in grants to groups developing phage-based therapies.

As an MD-PhD student, Lu gravitated toward phage engineering after learning about the problem of antibiotic resistance. "I thought it was crazy we didn't have a solution," he recalls. In advisor James Collins's lab at Boston University, Lu "got really intrigued by phages. They had this weird vibe of being an old technology but with this whole new toolset."

Collins and Lu showed that phages can break up biofilms, stubborn webs of bacteria and extracellular matrix that immune cells and antibiotics have difficulty penetrating. Modifying the phages to deliver genes into bacteria to enhance the activity of antibiotics and adding enzymes from other phages that "chew up" biofilm matrices produced even better results. Harking back to d'Hérelle, in 2019 Lu and colleagues at Massachusetts General Hospital built an intestine organoid and showed how a phage they'd isolated from *Shigella* vanquished infection.

Phages' potential is vast, but finding the right ones isn't easy. Each case requires combing through meager phage libraries or sampling places where the bacterium lives, such as in sewage. Often, the hunt fails or yields phages that are difficult to work with. Synthetic biologists like Lu would love to prompt one type of phage to open multiple bacterial doors, but there's limited space inside phage "bodies" to cram genetic keys. Though these hurdles and more lie ahead, Lu and others in the field are optimistic that they're surmountable.

Not in my human

Another group of researchers is interested in viruses that infect humans without causing disease and then fend off more dangerous viruses and bacteria. GB virus C, an asymptomatic blood-borne virus, slows progression to AIDS in people with HIV and lowers the risk that infection with Ebola virus will prove deadly. Mouse studies suggest that certain innocuous herpesviruses and cytomegaloviruses prevent infection by *Listeria* and *Yersinia pestis*, which causes bubonic plague. Even harmful viruses can harbor disease-combating strategies for scientists to adapt. The hepatitis A virus can protect against hepatitis C, and researchers have used lymphoma-associated viruses to cure type 1 diabetes in mice.

Proponents lament that human viruses remain underexplored as infection fighters. "Medicine may benefit from taking mutualistic viruses more seriously," reads a 2011 article in *Nature Reviews Microbiology* titled "The good viruses."

Oncology has had better luck. Records spanning millennia tell of unusual cases where infection with what we now know to be viruses that cause diseases such as influenza, chicken pox, and measles temporarily beat back people's cancers. After a century of attempts with sometimes disastrous results, researchers in the past decade have succeeded in safely wielding viruses to cure or curb cancers or sensitize tumors to other therapies.

Oncolytic viruses—from onco, meaning mass or tumor, and lysis, to break apart—work by killing cancer cells and by helping the immune system do so. Unlike chemotherapy, radiation, and surgery, oncolytic viruses go after cancer cells while largely sparing healthy cells. Researchers defang the viruses so they don't cause disease themselves and can engineer them to deliver molecules that draw immune cells to the tumors.

The only oncolytic virus approved in the United States, called T-VEC, earned FDA clearance in 2015. It's a modified herpesvirus injected into late-stage melanomas in the skin and lymph nodes. Dozens of other candidates are being tested for treatment of numerous cancers. They may work solo, in tandem with conventional treatments, or when combined with advanced immunotherapies such as checkpoint inhibitors. The main challenge, researchers say, is stopping the immune system from destroying the viruses before they do their work.

"When I started my PhD, clinicians thought we were nuts for wanting to put viruses into people," says Lu. "Now it's a totally different world. People have seen that this type of engineering can transform patients' lives."

Even harmful viruses can harbor disease-combating strategies for scientists to adapt.

Your package has been delivered

Cepko went to college in the '70s and fell in love—with viruses.

"I appreciated their wiliness, their different life cycles, their ways of escaping host surveillance," she says. "I thought they were super interesting and valuable to study."

All that viral variety serves one goal: to latch onto cells, inject them with DNA or RNA, and turn those cells into virus copy machines. As doctors and scientists sought new and better ways to get treatments into patients' cells, particularly newfangled gene therapies, Cepko joined them in asking why not take advantage of viruses' innate skills.

Now, after decades of trial and error, viruses have become indispensable medical delivery vehicles.

"Gene therapy would be way, way, way behind if we didn't use viruses and viral vectors," says Cepko.

Researchers first disarm the virus by removing some or all of its genome from inside the virus's protein shell, or capsid. They might tweak capsid proteins to generate less of an unwanted immune attack or to home in on certain cell types. Then they fill the hollowed-out capsid with whatever they want to insert into cells, be it a healthy copy of a defective gene, genome editing machinery, a drug, or a vaccine.

The FDA issued its first gene therapy approval in 2017. Additional approvals have followed, and clinical trials have shot up into the thousands. So far all the gene therapies licensed worldwide, which have saved the lives of tens of thousands of adults and children with otherwise untreatable and often terminal diseases, use viral vectors in some way.

Hollowed-out adenoviruses and adeno-associated viruses, or AAVs, are the most popular choices for injecting healthy genes into the body. That's how approved gene therapies for spinal muscular atrophy and a form of inherited vision loss known as retinal dystrophy work. Cepko's lab has engineered AAVs to deliver gene cocktails into the eye to mop up inflammatory, oxidative, and metabolic damage caused by hereditary

retinal degeneration. The therapy has successfully prolonged vision in mouse models. This spring, the lab partnered with a biotech company that secured the retinal dystrophy approval to take Cepko's therapy forward.

"We haven't treated people yet, so I can't really say, but I would be very proud if we could help anybody retain their vision for any amount of time," she says.

When researchers want to change the genomes of cells permanently, such as to teach bone marrow stem cells to make nonsickled hemoglobin, they turn to modified lentiviruses and retroviruses: viruses that don't just inject free-floating genetic material into the cell nuclei they infect but actually integrate their genes into a host cell's DNA. These treatments take place outside the body. In the FDA-approved CAR-T cell therapies that revolutionized cancer treatment in recent years, clinicians retrieve T cells from the blood of patients with particular types of cancer and send the cells to a lab, where technicians use viral vectors to deliver a gene that helps the cells attack that cancer. The augmented T cells are then multiplied and reinfused into the patient. Similar strategies are being explored for blood disorders, HIV/AIDS, and dozens of other conditions.

Although promising, viral vector-based gene therapies still present challenges. Capsid proteins sometimes instigate immune response. As with phage capsids, AAV capsids have limited cargo space. Viral vectors introduced systemically accumulate in the liver, with only a small percentage reaching the tissues that need treatment. The low uptake means patients must receive massive doses to get enough vectors where they're supposed to go, which can cause fatal liver toxicity. Finally, costs are astronomical—up to $2 million per treatment—raising concerns about equitable access.

Tabebordbar and collaborators may at least have solved the liver issue for the treatment of genetic muscle diseases.

Personal inspiration

Tabebordbar grew up watching his father slowly lose muscle strength and coordination from a rare genetic disease. The decline motivated Tabebordbar to become a scientist and pursue treatments for muscle-wasting conditions. His PhD advisor, Amy Wagers, the Forst Family Professor of Stem Cell and Regenerative Biology at Harvard and HMS, inspired him to seek solutions in gene therapy.

Some estimates hold that bacteria in and on our bodies outnumber our own cells 10 to 1. Some scientists say we may harbor a tenfold greater number of viruses.

The breakthrough came when Tabebordbar was a postdoctoral fellow in the lab of Pardis Sabeti, MD '06, a professor of organismic and evolutionary biology and of immunology and infectious diseases at Harvard and a member of the Broad Institute of MIT and Harvard. Tabebordbar and a pan-Harvard team including Sabeti and Wagers generated more than 5 million slightly differing AAV capsid variants and introduced them into animal models. They identified the 30,000 capsid types that reached muscle tissue, evolved those into new variations, and identified a family of capsids that zeroed in on muscle and mostly bypassed the liver. The vectors, dubbed MyoAAV, worked at one-hundredth the doses currently given to people. The team published the results in September 2021 in *Cell*.

The work gives researchers a protocol for developing liver-sparing AAV capsids that reach tissues other than muscle. Sabeti's group has already attempted one for the central nervous system, which Cepko is testing in the retina. Tabebordbar, meanwhile, spun off a company to take MyoAAV to human trials and now serves as its chief scientific officer. Although his father's disease has progressed too far for him to benefit, Tabebordbar hopes the therapy will prove safe and effective for thousands of others with genetic muscle disorders.

"It's exciting to engineer these viruses to develop technologies that can help humanity," he says.

Viral vectors also have become a hot topic for researchers developing vaccines. Half a dozen have been approved worldwide, all targeting SARS-CoV-2 or Ebola virus. Among them is Janssen Pharmaceuticals' COVID-19 vaccine, the development of which drew upon years of work by Dan Barouch, MD '99, the William Bosworth Castle Professor of Medicine at HMS and Beth Israel Deaconess Medical Center. Barouch had been working on an AAV-based vaccine for HIV, then redirected the project when the new pandemic struck.

Researchers are testing other viral vector-based vaccines for intractable pathogens, including Zika virus and malaria parasites. Bacteriophages may aid in this arena, too. A team including Richard Sidman, MD '53, the HMS Bullard Professor of Neuropathology, Emeritus, published a proof-of-concept study in *PNAS* in 2021 showing the promise of using phages to deliver COVID-19 vaccines.

Long-term tenants

Astronomer Carl Sagan used to say, "We are made of star stuff." Recent years have shown that we are also made of microbes. Some estimates hold that bacteria in and on our bodies outnumber our own cells 10 to 1. Now scientists say we may harbor a tenfold greater number of viruses.

The rise of metagenomic sequencing in the past fifteen years has allowed scientists to identify a good chunk of the viruses that comprise our virome, says NIH's Koonin. Understanding what those viruses are doing should follow. Early studies suggest that while some cause damage or await opportunities to do so, others do us favors, including modulating our microbiomes and fighting off invaders. Such findings have led to speculation that manipulating the virome could help treat gastrointestinal and mood disorders.

Other viruses go deeper, down to our DNA. Every so often in the far recesses of history as humans and our evolutionary forebears evolved, a retrovirus infected an egg or sperm cell; that cell became a fertilized embryo that developed to term with viral DNA incorporated everywhere; and the resulting offspring went on to have offspring of their own, passing the DNA through subsequent generations. According to Koonin, about 50 percent of our genome once belonged to viruses and related mobile genetic elements.

Most of the viral gene remnants, or endogenous retroviruses, studied so far have proven either inert or latent, lurking until they reawaken and contribute to disease. An unknown number, however, were evolutionarily repurposed for our benefit. Mounting evidence suggests that



JAY WATSON

endogenous retroviruses spurred the rise of placental mammals. Genes derived from viruses make proteins that form a foundational layer in the placenta and regulate a hormone that controls birth timing in primates. In the nervous system, endogenous retroviruses appear to contribute to brain development, long-term memory formation, and neuronal communication. Our once-viral genes also may influence immune function, embryonic development, and "probably a number of things we are not fully aware of yet," says Koonin. More will surely resolve as researchers peer closer.

Evolution engines

The viruses that threaten humans and the animals and plants we're familiar with barely register among the estimated 10^{23}-10^{31} virus particles that dominate our planet, most of which stay busy infecting other microbes. Their effects on cellular life run deep.

Viruses cull microbes around the world in incredible numbers every day, creating sediment that sustains food chains, providing nutrients for photosynthetic marine organisms that produce half the world's oxygen, and helping power carbon, nitrogen, and phosphorus cycles.

"Viruses basically regulate ecology and biogeochemistry on a global level," says Koonin.

The so-called arms race, in which viruses spur hosts to develop antiviral defenses that then incite viruses to overcome those defenses and so on, represents one of the most powerful drivers of evolution on Earth, Koonin says, as do viruses' abilities to transfer genes among one another and from host to host.

Although it seems intuitive that if viruses need cells to replicate, then they must have evolved after cells, observations and computational analyses have led a group of researchers including Koonin to the conclusion that certain building blocks of viruses predated the development of cellular life. Protoviral elements in the primordial soup formed RNA and DNA and ultimately laid the path for the evolution of cells, Koonin explains. Later, cells provided proteins for structures such as capsids; viral elements began to co-opt cells for replication; and modern viruses arrived.

"The emergence of complex life would not have been possible without contributions from genetic parasites in general and viruses in particular," Koonin says.

From the origins of life to technologies that preserve it, learning about viruses can transform people's opinions on what once seemed like straightforward agents of disease and death.

"When I hear the word virus, I'm not scared anymore," says Tabebordbar. "I ask, 'Okay, what type of virus? What does it do? What are the implications?'"

Even as their lives and careers warp around a pandemic virus, he and colleagues worldwide continue to unveil the good that viruses can do.

Stephanie Dutchen is manager of feature content and multimedia in the HMS Office of Communications and External Relations.

Noise pollution is more than a nuisance. It's a health risk

By Stephanie Dutchen



Airplanes pierce the night. Leaf blowers interrupt fall mornings. Quiet gives way to air conditioners, pounding music, construction equipment, street traffic, barking dogs, sirens.

For half a century, U.S. agencies such as the EPA have deemed noise pollution "a growing danger to the health and welfare of the Nation's population." The European Environmental Agency reports that noise ranks second only to air pollution as the environmental exposure most harmful to public health.

Yet, in sectors from government regulation to health care practice, the threats posed by noise remain "often underestimated," according to the International Commission on Biological Effects of Noise.

Researchers and clinicians are trying to change this. They've shown that noise pollution not only drives hearing loss, tinnitus, and hypersensitivity to sound, but can cause or exacerbate cardiovascular disease; type 2 diabetes; sleep disturbances; stress; mental health and cognition problems, including memory impairment and attention deficits; childhood learning delays; and low birth weight. Scientists are investigating other possible links, including to dementia.

Research also reveals how noise pollution connects with climate change. Many contributors to global warming generate noise, chief among them transportation and fossil fuel extraction and processing. Urban sprawl and deforestation destroy natural carbon absorption reservoirs while removing natural sound buffers. Technologies that help people deal with climate change, like air conditioners and generators, can be noisy. Conversely, certain climate mitigation strategies such as creating green spaces in concrete jungles offer opportunities to muffle noise.

Wanted: better models

Estimates hold that chronic noise exposure contributes to 48,000 new cases of heart disease in Europe each year and disrupts the sleep of 6.5 million people. Quantifying noise pollution's contribution to health problems and death in the United States, however, remains a challenge because of poor measuring and monitoring, says Peter James, an HMS associate professor of population medicine in Harvard Pilgrim Health Care Institute's Department of Population Medicine. This makes it harder to determine the best policies and medical practices for care.

"The U.S. hasn't really funded noise control or noise research since the 1980s," says James. "It's a big problem. We need to prioritize this so we can really pin down how noise affects health."

James helps colleagues apply existing noise modeling data to large cohort studies, such as the Nurses' Health Study, to analyze participants' noise exposures and health outcomes. The models have low resolution, however, and working with them can be frustrating: researchers can't be sure whether a negative finding means noise doesn't contribute to a particular outcome, such as something as seemingly unrelated as menopause onset, or the data weren't robust enough to reveal a connection. James hopes to augment epidemiological data with input from participants using sensors and apps, which can deliver precise location and health information.

"Given what we do know, noise is too significant an issue for us to sit around and wait to have perfect data," he says.

James led a seminal 2017 study, published in *Environmental Health Perspectives*, which shows that people in neighborhoods with low socioeconomic status and higher proportions of residents of color bear the brunt of noise pollution in this country.

"We want our patients to reduce their exposure as much as possible, such as wearing ear plugs or investing in soundproofing insulation, but that's not possible for many who live in the noisiest areas," he says. "To say the onus is on the individual to fix their noise exposure is not feasible."

Heart, felt

Another branch of inquiry focuses on how vibrations from noise can cause impairments. Part of the answer lies in the stress-response system. Researchers have found that the more people are bothered by noise, the greater the health risks they face from it. Yet, even those who tune out noise pollution, whether when awake or asleep, experience autonomic stress reactions.

Ahmed Tawakol, an HMS associate professor of medicine at Massachusetts General Hospital, and Michael Osborne, an HMS instructor in medicine at Mass General, have used advanced PET scanning to show that transportation noise is associated with heightened activity of the amygdala relative to regulatory cortical regions. Amygdalar activity can trigger stress pathways, including inflammation, that can lead to cardiovascular and metabolic diseases. Participants with a higher ratio of amygdalar to cortical activity had more risk for adverse outcomes in follow-up. The link persisted even after accounting for other disease risk factors.

In the clinic, Tawakol and Osborne say that evidence supports strategic intervention rather than trying to squeeze questions about noise into each patient encounter.

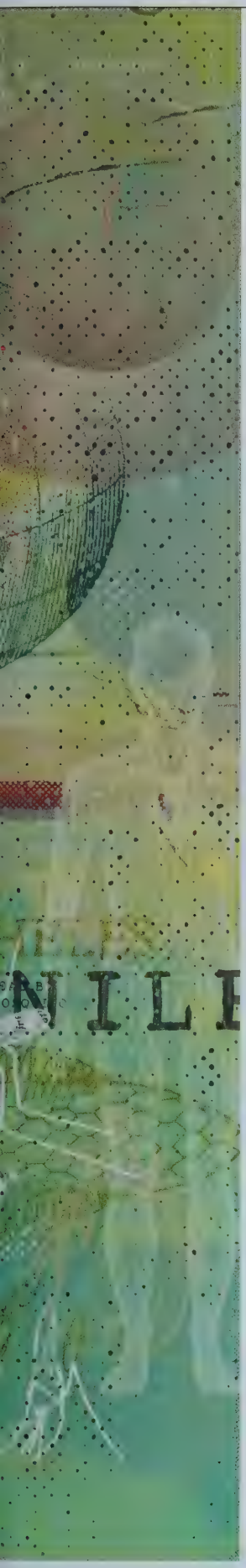
"If a patient mentions noise as a cause of stress, especially if they have or are at risk of cardiovascular disease, I'd certainly recommend personal noise mitigation strategies and stress reduction techniques," Osborne says.

As researchers reveal the mechanisms and magnitude of noise-induced illness, clinicians will become better equipped to identify at-risk patients and prescribe effective solutions.

Stephanie Dutchen is manager of feature content and multimedia in the HMS Office of Communications and External Relations.

MEROVINGIAN/DIGITAL VISION VECTORS/GETTY IMAGES


MALARIA
MOSQUITO VECTORS (ANOPHELES) THAT TRANSMIT THE MALARIA PARASITE, PLASMODIUM SPP.
VIRUS
HEAD
THORAX
AEDES TAENIORHYNCHUS
ANOPHELES
AEDES AEGYPTI
ZIKA
WEST



DUNG HOANG

Climate change is providing opportunities for insects and other animals to spread infectious diseases to new populations

Double Jeopardy

BY CHARLES SCHMIDT

IN SEPTEMBER 2018, GAURAB BASU received an email alerting him that one of his patients, a man in his late 60s, had just been hospitalized with unexplained fever and confusion. Basu, an HMS instructor in medicine, primary care physician, and co-director of the Center for Health Equity Education and Advocacy at Cambridge Health Alliance, suspected that his patient might have an infection, but the cause was unclear. "It took some real detective work to figure out what it was," Basu says. A lumbar puncture finally pinpointed the source of his patient's malaise: West Nile virus, a mosquito-borne pathogen more common to the tropics than New England in early autumn. Basu had never encountered the virus in any of his patients and says the diagnosis "came as a real surprise."

All over the world, doctors like Basu are contending with the consequences of significant changes in the distribution and prevalence of vector-borne infectious diseases. West Nile fever surfaced in the United States in 1999 and has since become the country's most common mosquito-borne illness, affecting thousands of people every year. The disease is also spreading into Europe, along with other mosquito-borne diseases such as dengue and chikungunya, while in Africa malaria is moving into higher elevations.

Tick-borne diseases are also on the move. Cases of Lyme disease, anaplasmosis, and Powassan encephalitis have more than doubled throughout the United States throughout the past two decades, as the ticks that transmit these illnesses expand into new areas, according to Ben Beard, deputy director of the Division of Vector-Borne Diseases at the U.S. Centers for Disease Control and Prevention in Fort Collins, Colorado.



Several factors explain these trends, not least among them demographic and land-use changes that bring people and infectious disease vectors closer together. "But many models suggest that temperature is a dominant driver," says Jason Rohr, an infectious disease biologist and chair of the Department of Biological Sciences at the University of Notre Dame.

Critical aspects of a vector's lifecycle, such as its growth, reproductive capacity, and biting rates, are temperature dependent. Temperature also influences rainfall patterns that in turn affect vector habitats. In general, mosquitoes lay eggs in standing water, and ticks thrive in humid weather. For them, "drought is death," says Sam Telford, professor of infectious disease and global health at the Cummings School of Veterinary Medicine at Tufts University.

As global mean temperatures rise steadily with climate change, efforts to model and predict future trajectories for vector-borne diseases are taking on a new urgency. Climate "profoundly influences the effectiveness of different kinds of health interventions," says Matthew Bonds, an associate professor of global health and social medicine in the Blavatnik Institute at HMS. "By modeling the complex interactions of multiple hosts, viruses, and temperature, we seek to identify the most effective strategies for reducing the risk of disease emergence."

Temperature creep

That climate contributes to the spread of infectious diseases has long been known. In ancient Rome, for example, aristocrats would retreat to hillside resorts in summer to avoid malaria, a disease whose name derives from the Latin mal + aria, or "bad air."

Now climate change is affecting the infectious disease landscape in profound ways. Greenhouse gases resulting from the burning of fossil fuels have pushed mean global temperatures higher by just over 1°C since 1850. If the most recent projections from the United Nations Intergovernmental Panel on Climate Change (IPCC) hold true, global average temperatures could rise by

more than 1.5°C over the next 20 years, leading to dramatically higher sea levels; longer and more frequent heat waves; and extreme weather events, which are unusually severe weather or climatic conditions that, according to the U.S. Department of Agriculture, devastate communities and agricultural and natural ecosystems.

According to the IPCC, each incremental increase in global temperatures will lead to more deaths from infectious diseases and other causes. Yet not all vector-borne diseases will respond in the same way, or uniformly, to increases in mean global temperatures, says David Relman, MD '82, the Thomas C. and Joan M. Merigan Professor in Medicine and professor of microbiology and immunology at Stanford University. As the climate warms, "a disease that becomes more prevalent and severe in one place may become less so somewhere else and another may reveal a different temporal and geographic pattern," he notes. In 2008, Relman was the chair of the National Academy of Sciences panel that examined how climate change and extreme weather could affect the emergence of infectious diseases.

Rohr agrees, adding that many scientists have abandoned what was once a basic assumption in infectious disease modeling, namely, that a vector's performance, that is, its capacity to thrive and infect people, increases linearly with rising temperature. Current models, Rohr says, which capture nonlinear relationships between warming and performance better than previous models, show that transmission of disease increases with rising temperatures—up to a point. Excessive heat beyond what vectors and pathogens can tolerate can slow transmission "and then diseases begin to decline," Rohr says.

Peter Hotez, dean for the National School of Tropical Medicine and professor of pediatrics and molecular virology and microbiology at Baylor College of Medicine, points out that in certain parts of east Africa, skyrocketing temperatures and diminishing rainfall patterns are adversely affecting the mosquitoes that carry malaria and the snails that carry schistosomiasis. Yet temperature increases at higher elevations may create new niches for vector-borne pathogens, further contributing to the redistribution of mosquito- and snail-borne diseases.

Rohr and his colleagues recently published modeling results showing that the transmission of West Nile and five other mosquito-borne viruses peaks between 23°C and 26°C before dropping off as temperatures increase. According to the model's predictions, transmission seasons will lengthen where cooler areas get warmer and contract in areas where the current temperatures already bump up against the vectors' thermal limits. The model also shows that warming can boost transmission in higher elevations, where cool temperatures ordinarily keep vector populations in check.

Temperature increases at higher elevations may create new niches for vector-borne pathogens.

That is concerning especially for malaria transmission risk in the highlands of east Africa, which stretch over an area the size of Egypt south of the Sahara desert. Reaching heights of at least 1,500 meters, the highlands tend to be cool, with daily mean temperatures below 20°C. Malaria transmission occurs only seasonally in the region, and because of that, people who reside there are less likely to build an immunity to the disease than people in lower-lying areas where infections occur year-round.

With climate change, however, "I think malaria transmission in the highlands will increase," says Marcia Castro, Andelot Professor of Demography and chair of the Department of Global Health and Population at the Harvard T.H. Chan School of Public Health. "Over time, those areas will become more susceptible to the mosquito vector staying longer than just a few months of the year."

Predicting how warming affects malaria transmission is challenging, however, because climatic pressures often occur in tandem with land-use changes and health interventions that affect local disease rates. Indeed, deaths from malaria declined 40 percent in Africa between 2000 and 2015, largely because of the expanded use of insecticide-treated bed nets.

While a postdoc at the Harvard Chan School, Pamela Martinez, now an assistant professor of microbiology and statistics at the University of Illinois Urbana-Champaign and a visiting scientist at the Chan School, collaborated on a project to isolate the effects of temperature on the number of malaria cases in the highlands of Ethiopia. Malaria cases had surged in the highlands during the 1970s but by the beginning of the twenty-first century, the number of cases in the region had mysteriously fallen off. Martinez and her colleagues knew that efforts to protect local populations from infection had ramped up only in 2005, years after the incidence had begun trending downward. So public health interventions were not the likely reason for the decrease.

As it happened, however, the slowdown coincided with a multiyear pause in global

"A disease that becomes more prevalent and severe in one place may become less so somewhere else and another may reveal a different temporal and geographic pattern."

warming between 1998 and 2005. During that time, mean global surface temperatures hardly budged, a phenomenon that scientists now attribute to transient and unusually strong oscillations in oceanic currents—El Niño in 1997-1998 and La Niña in 1998-1999—that led to the sea absorbing more heat from the atmosphere than normal.

Martinez and her colleagues suspected that the pause in global warming and the slowdown in malaria transmission were connected. Regional climate records confirmed that local temperatures had dropped in tandem with global averages during the period. When they modeled the data, the scientists found that climate conditions and the decrease in malaria cases were strongly coupled. Martinez says the findings underscore the crucial role of temperature in driving the incidence of malaria either lower or higher.

Warming also expands opportunities for disease transmission by other tropical pathogens, such as the Zika virus. Transmitted by the *Aedes aegypti* mosquito, the Zika virus had been common only in a narrow equatorial range in Africa and Asia. After 2007, however, the virus began spreading eastward across the Pacific Ocean. Since then, more than 80 countries have reported Zika outbreaks. An outbreak that began in Brazil in 2015 led to an estimated 1.5 million infections in that country before spreading elsewhere in the Americas. Zika typically produces mild symptoms, such as fever, rash, and muscle aches, but, in rare cases, patients can develop Guillain-Barré syndrome, a condition that drives immune cells to attack the nerves. Furthermore, infection with Zika during pregnancy can lead to debilitating birth defects, including microcephaly, in which the head and brain are abnormally small.

Bonds and his colleagues recently published a modeling study suggesting that in a worst-case scenario, 1.3 billion more people would live in temperature conditions suitable for Zika transmission by 2050. That scenario assumes that fossil fuels will be burned at ever-increasing rates. "It's amazing how fast Zika takes off when temperatures are suitable for the mosquito vector," says Bonds, who has doctoral degrees in ecology and economics. "Our models show it spreading like wildfire." Bonds predicts that people living in most of the southern United States will over time face higher risks not only for infection by the Zika virus, but for infections by related flaviviruses in the same genus, including those that cause West Nile, dengue, and yellow fever.

The CDC estimates the average number of Lyme cases diagnosed and treated in the United States at 476,000 per year between 2010 and 2018, up from a yearly average of 329,000 between 2005 and 2010.

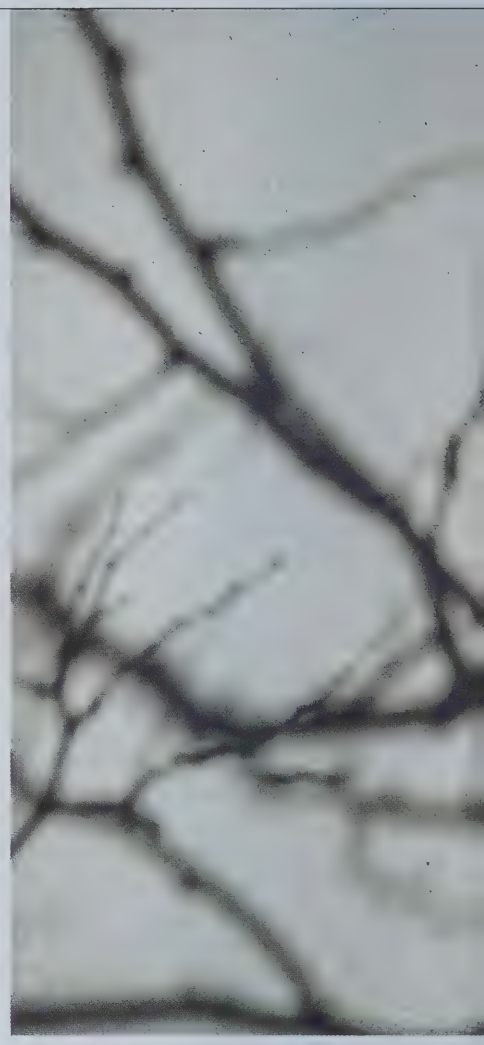
Unwelcome uptick

Meanwhile, the incidence of diseases carried by an entirely different sort of vector—ticks—is exploding across the United States. According to Beard at the CDC, the number of cases of Lyme disease in the United States reported annually to the CDC recently approached 40,000. But busy doctors and public health workers often don't have time to report Lyme disease cases, Beard says, so the real number is likely higher.

That likelihood seems feasible, based on case estimates from insurance claims data. The CDC estimates the average number of Lyme cases diagnosed and treated in the United States at 476,000 per year between 2010 and 2018, a substantial increase over the annual average of 329,000 cases documented in insurance claims between 2005 and 2010. The rise in numbers parallels corresponding increases in the geographical distribution of ticks that carry Lyme and other diseases. Tick populations are moving steadily north, and species appearing in different parts of the country are also changing.

"In the past twenty-five years," says Beard, "the number of counties in which the blacklegged tick, which transmits the Lyme pathogen, *Borrelia burgdorferi*, has become established has more than doubled. The lone star tick, a vector for ehrlichiosis that was once limited largely to the southern United States, is now found all the way up into New England."

Research indicates that many factors other than climate affect how ticks spread and come into contact with people. For instance, ticks prefer forest habitats, which



in the United States have grown back following the steady decline in land cleared for agriculture since the 1800s. Thanks to conservation laws, white-tailed deer populations, which are reservoirs for ticks in the wild, have rebounded from about half a million in the early 1900s to more than 25 million today.

Human activities that influence disease risk are also changing. As suburban sprawl continues unabated, more people are spending time outdoors, where they face higher risk of infection. Beard agrees that climate change explains in part why ticks are spreading northward, but in other parts of the country, land use and human behavior play greater roles.

The human variable

Telford, who specializes in the ecology and epidemiology of tick-borne illnesses, also thinks humans play a significant role in disease risk. In a recent expert opinion in a book on climate, ticks, and disease published by CABI, an international organization dedicated to applying scientific expertise to problems affecting



Marcia Castro

JOHN SOARES

agriculture, Telford wrote that "human aspects of transmission risk are still poorly studied and need to be considered in any discussion of the role of climate change on vector-borne infections." Cases of dengue fever in Mexico, he says, outnumber those in nearby parts of Texas "because Americans are more likely to have air-conditioning and stay inside, even though the mosquito habitat and breeding are identical on either side of the border."

Echoing points raised by Relman at Stanford, Telford speculates that climate change may not in fact generate net increases in vector-borne disease rates, assuming that rising cases in some areas are matched by declines in others. "You wind up with a shifting of the risk of disease," Telford says. "The cases overall balance out."

Still, social determinants and climate change can conspire to drive disease patterns in unexpected ways. Hotez cites a notable example: unprecedented temperatures of up to 50°C in the Middle East are fueling droughts that affect ancient agricultural lands, driving people to the cities, where crowding and urbanization, together with political instability, can lead to conditions that affect the rates of illness. In Aleppo, Syria, conflict has undermined infrastructure, resulting in, among other things, uncollected garbage that provides a breeding ground for sandflies that transmit a disfiguring illness called cutaneous leishmaniasis. The illness is becoming more widespread in the region.

Droughts affecting agricultural lands in the Middle East are driving people to the cities, where crowding and urbanization, together with political instability, can lead to conditions that affect illness rates.

Land-use changes can elevate disease risk by altering susceptibility to mosquito breeding, as shown by how deforestation in the Brazilian Amazon contributes to increases in malaria. Also, as new cities emerge in the Amazon, so do areas affected by dengue.

Castro does much of her field work in the Amazon, where her research focuses on mosquito-borne diseases. She says that climate change has the potential to expand areas suitable for the presence of mosquitoes and contribute to what she says are intensifying disease risks, which in many places are characterized by more frequent disease outbreaks.

"The math is a lot more complicated than simply putting in a climate variable and then assuming it's going to lead to a doubling or tripling of cases of a disease like malaria," Castro says. "When trying to simulate a future in which the climate is changing, you have to account for the underlying local context and epidemiology."

Meanwhile, back in Massachusetts, Basu says clinicians need to be ready for surprising diagnoses and infectious diseases they might not otherwise expect to see. His West Nile patient eventually recovered but only after a long slog that took the better part of a year. "I tell my medical students that we need to keep monitoring and understanding the implications of global warming on our own practices. This is a dynamic process and things are changing."

"The math is a lot more complicated than simply putting in a climate variable and then assuming it's going to lead to a doubling or tripling of cases of a disease like malaria."

Charles Schmidt is a writer based in Maine.



Social media should promote conversation and exchange, yet increasingly it creates echo chambers that isolate

By Elizabeth Gehrman



Heard Immunity

THOUGH THE UNITED STATES accounts for only about 4 percent of the global population, it leads the world in COVID-19 cases and deaths, and among high-income countries is behind only Russia in vaccine opposition. Studies find that anywhere from 8 to 22 percent of the population remains unwilling to get jabbed, despite the reams of data and anecdotal evidence showing the shots are overwhelmingly safe and effective.

Early in the pandemic, this hesitancy could have been partly accounted for by the fact that "denial and superstition are typical human responses to plague," according to Nicholas Christakis, MD '89, director of the Human Nature Lab at Yale University and co-director of the Yale Institute for Network Science. But a larger effect comes from the ways in which behaviors, attitudes, and emotions spread among members of a group, moving as fast as and often as virulently as any biological pathogen. A 2021 study by the Center for Countering Digital Hate, an international nonprofit that works to stop online hate and misinformation, showed that two-thirds of content opposing vaccines and vaccination shared on Facebook and Twitter originated from just 12 people, which is in keeping with research Christakis has done on how information advances through time and space.

"A very deep and fundamental principle of human social networks is that they magnify whatever they are seeded with," Christakis says. "They don't give rise to things. But once you put something into the network, the network will make more of it. If you put Nazism into the network you get more Nazis; if you put love into the network you get more love. If you put anti-vaccine sentiment into the network, what's going to happen?"

All together now

Social scientists first postulated that relationships matter to an individual's health in the late 1800s, but it wasn't until 2009 that the all-encompassing effects of relationships entered the public consciousness, as a result of Christakis's book *Connected*, co-written with James Fowler, a political scientist at the University of California San Diego. In it, the authors show how people you don't even know influence nearly every aspect of your life, from behaviors like smoking, drinking, voting, cooperation, and divorce to conditions like obesity to attitudes like happiness or vaccine acceptance. "If your friends are obese, your risk of obesity is higher," Christakis explains in a 2010 TED Talk. "If your friend's friends are obese your risk of obesity is 25 percent higher." It's only when you get to your friend's friend's friend's friends, he continues, "that there's no longer a relationship between that person's body size and your own body size."

This association could be due to homophily, in which birds of a feather flock together, so to speak, or to confounding, in which you and your friend's friends might share a common exposure to, say, a new pizza place down the street. A key effect, however, comes from induction, in which weight gain becomes a norm—it's simply more acceptable within the group. "We found that if your friend becomes obese it increases your risk of obesity by about 57 percent in the same given time period," Christakis says. Recognizing some of the possible ramifications of these findings, Christakis points out it would be a misuse of the findings to justify prejudice against people with larger body sizes.

In the 1960s the Harvard social psychologist Stanley Milgram showed that we are each separated by an average of six connections from everyone else in the world.

The more Christakis and Fowler studied social networks, the more they came to see them as living things independent of the individuals who comprise them. "This network that's changing across time has a memory," Christakis says in the TED Talk. "It moves; things flow within it. It has a kind of consistency; people can die but it doesn't die. … It has a kind of resilience that allows it to persist across time." In the 1960s the Harvard social psychologist Stanley Milgram showed that we are each separated by an average of six connections from everyone else in the world. To that proposition, which inspired the 1990 play *Six Degrees of Separation* and the 1993 film of the same name, Christakis and Fowler added the finding, since replicated many times over, that we each have three degrees of influence—on our friends, their friends, and their friends' friends.

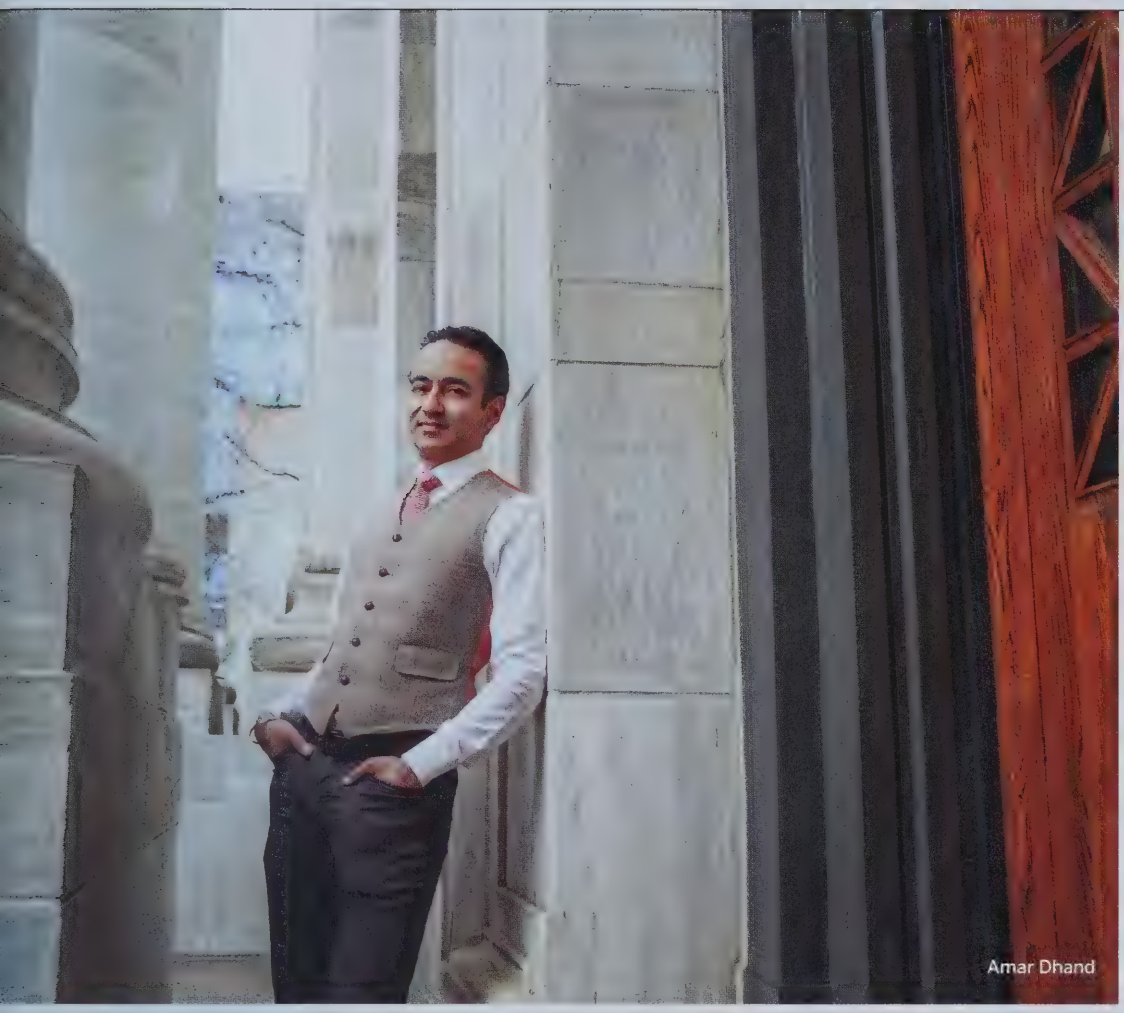
Hive behavior

"Human brains are designed to function in concert with other human brains," says Ian Corbin, an HMS research fellow in neurology at Brigham and Women's Hospital, co-director of the hospital's Human Network Initiative (HNI), an interdisciplinary research center, and senior fellow at Capita, a think tank. "That is our optimal form of cognition, and if you pull us out of social contexts of intersubjective feedback loops, our brains have to work harder."

Amar Dhand, MD '08, an HMS associate professor of neurology and Corbin's co-director at HNI, explains how this came about. For millions of years, when population numbers were low, hominid brains grew steadily larger, until around the Neolithic period in the Stone Age, when complex societies began to emerge. "The Neolithic human brain shrank compared to its evolutionary ancestors, while perhaps becoming more sophisticated internally to maintain cognitive capacity," Dhand says, adding that the metabolism and energy that might have been required by a larger brain could then be reallocated to endurance and other adaptive functions. "Neolithic humans had to be hyperaware of threats because they were in very small groups or maybe alone in the wild most of the time, which would create an incredible stress response," he says. "The fact that you could now be interdependent and rely on friends to be watching for threats too would reduce your cortisol level and contribute to an increased life span for the next step on the evolutionary tree."

Social networking also frees up energy previously devoted to cognition. "If you're a trusted co-perceiver of mine," Corbin says, "then my brain has to do less work than if I have to arrive at solutions by myself." And it allows for behaviors that can be understood only by studying the collective, Christakis points out, as when a hive of bees finds a new nesting site or a school of fish evades a predator. Examples like this, he says, "require a complicated mix of dense ties that are designed to reinforce shared knowledge

"Human brains are designed to function in concert with other human brains. That is our optimal form of cognition."



Amar Dhand

JOHN SOARES

and practices, but also loose ties that allow access to dissimilar knowledge. The ability to exploit your environment is enhanced by your close ties. But what happens when the well goes dry and no one among us knows where new water is to be found? There has to be a trade-off between intensity and novelty, and networks have optimized that."

Real/unreal/constructed

"All reality is social reality," writes Jay Van Bavel, an associate professor of psychology and neural science at New York University, in his book *The Power of Us*, coauthored with Dominic J. Packer, a professor of psychology at Lehigh University. But how do individuals come to identify with the thinking of a particular group?

"Children develop their understanding of the world in a feedback loop with their caregivers," Corbin says. "Staying embedded with people who share your assumptions is the easiest and most comfortable thing. Sometimes this begins to change when you start to see the world and have other experiences. You might look around and be like, 'I think my parents and their community are missing some stuff. My friends at school seem to get it.' That's when you may break off and go into other groups."

Not only do your circumstances at birth and your foundational friendships affect what you believe, but thanks to magnetic resonance imaging, scientists now know that your brain structure may play a role. While correlation doesn't necessarily equal causation, we know that environment can help shape brain structure.

A 2013 book, *Predisposed,* which investigates how people develop their political predespositions, discusses a *Current Biology* paper by scientists at University College, London. Using structural MRI to view brain activity in young adult participants, the researchers found that the volume of the amygdala, associated with the fight-or-flight response and encoding emotional memories, tends to be greater in people with conservative views, while the gray matter volume in the anterior cingulate cortex, associated with empathy-related responses and resolving emotional conflict, is greater in those whose views are more liberal.

Whatever the answer to the chicken-and-egg question may be, social media's exploitation of these opposing biological responses underlies, at least in part, the political polarization in the United States and other parts of the world. For many people, that polarization has become extreme enough to warrant the label "cultlike," Corbin maintains, with extreme beliefs existing on both ends of the political spectrum.

Social media's exploitation of opposing biological responses underlies, at least in part, the political polarizations in the United States and other parts of the world.

"What used to be subcultures are now in constant confrontation with each other because of cable news and the internet," Corbin says. "If I'm being bombarded by groups that think my worldview is totally wrong, that's threatening to me. So we circle the wagons. Why on God's green earth should a vaccine be a political issue? It only became one because each group feels a heightened threat level."

That these conflicts have increasingly played out online is "different quantitatively but not qualitatively" from real-life interactions, says Christakis. "Our desire for social connection and our susceptibility to its influence are not changed by new technologies," he notes, mentioning advances from the printing press to the telephone to, of course, social media. "It's just amplified."

Van Bavel agrees. "Our brains' facility at cooperating and coordinating was very successful for outcompeting other groups and species," he says. "But it also can lead to massive intergroup conflicts." He is quick to point out that much of the current outrage we see online is intentionally manufactured, in part to increase group cohesion. This is done in many ways, including the use of what Van Bavel calls moral-emotional language—words like *hate*, *shame*, *ruin*, *blame*, *attack*, and *wrong*.

Such words and tactics increase defensiveness among those receiving them, which can then lead those who first delivered the emotion-laden language to "double down," touching off a vicious cycle. "Making the people in your group feel that they have been attacked creates the perception that you are all under threat … and helps to generate a shared sense of identity," Van Bavel writes in *The Power of Us*. That shared identity, he says, "can affect all manner of psychological processes, including attention, memory, empathy, schadenfreude, and perception." He cites plenty of research showing he means perception literally as well as figuratively,

documenting many instances of groupthink affecting what people see, hear, taste, and smell, including a Princeton alumnus who thought the fouls his team made during a particularly rough game were taken from a tape, and a study that had students sniffing a dirty T-shirt: When the shirt bore a rival school's logo, students reported more disgust than for T-shirts from their own school.

A proper perspective

But the research isn't all bad news. While changing minds isn't easy, there are ways to counteract the chauvinistic tendencies engendered by group dynamics and also to use social networks to promote positive discourse and behavior. For example, as Van Bavel writes, although "most of the information people get about politics reinforces the idea of unbridgeable divides," when attitudes are objectively examined, it turns out the left and right are closer than one might think on controversial issues like health care, immigration, and gun control.

How information is presented matters. For instance, though election maps are starkly delineated in red and blue, a more accurate depiction would include shades of purple. When one study showed people more nuanced maps, the participants, Van Bavel writes, "stereotyped their political out-groups less and saw the United States as less divided."

Once misinformation is in circulation, fact-checking can be helpful, but whether it is effective depends largely on how it's presented and by whom. A 2019 study published in *Communication Research* by communications studies scholars Riva Tukachinsky of Chapman University and Nathan Walter of Northwestern University neatly summarizes the parameters necessary to make an impression: "Corrective messages were found to be more successful when they are coherent, consistent with the audience's worldview, and delivered by the source of the misinformation itself," the authors write. "Corrections are less effective if the misinformation was attributed to a credible source, the misinformation has been repeated multiple times prior to correction, or when there was a time lag between the delivery of misinformation and the correction."



Nicholas Christakis

In other words, if a member of your in-group tells you something, it's more likely to take hold. "One study told people that the head of the National Institutes of Health was a scientist and also a Christian," Van Bavel says. "They found the group hearing that was more likely to get vaccinated." But this doesn't always work, as former president Donald Trump discovered in December when he was booed for admitting he'd been boosted. That's because, Corbin says, "when you're confronted with a dissonant fact, either your worldview has to change or your perception of the fact has to change. We crunch numbers like that all the time without even realizing it, but when the fact challenges a nonnegotiable part of your worldview, it has to be wrong, even when you're seeing something with your own eyes."

On the upside, people can be accurate when they choose to be. Van Bavel cites one study in which participants were asked whether they would share controversial headlines, and many said yes largely because they were motivated by a goal such as needling the other side, amusing their friends, or getting online attention. When the same group was asked to consider accuracy when deciding, fewer admitted they would share the post.

Incentivizing evidence-based reasoning also works. While science, journalism, law, and some other professions reward this kind of thinking, social media doesn't—but with some effort, it could be made to. "People care a lot about social rewards," Van Bavel says. "If they could gain status by being accurate, they'd be more likely to share based on that." In research Van Bavel conducted with two colleagues, "simply offering participants a dollar for forming accurate beliefs was sufficient to reduce their partisan biases."

One reason people identify so strongly with online groups, sometimes to the exclusion of their own families, is declining trust. Since Gallup's Confidence in Institutions surveys began in 1973, trust in organized religion, government, public schools, and journalism has decreased significantly, with "the medical system" being one of the hardest-hit categories.

In 1975, 80 percent of respondents said they put a "great deal" or "quite a lot" of trust in medicine; last year only 44 percent did, a slight uptick from a low of 36 percent just before the pandemic. "If you have a trusted system of medical experts you don't have to go on the internet and find a bunch of wackos," says Corbin. "A lot of the mistrust is warranted, so people go scrambling for other things to trust"—in some cases in those who provide what Van Bavel calls symbols of trustworthiness without the integrity to back them up, as often happens online.

Corbin says he has no magic bullet for counteracting this massive crisis of authority systemically, but he does think that individuals, particularly physicians, can make a difference. "Trust is built on a pretty intimate level," he says, "and a lot of it is just treating people with respect and acknowledging up front that a lot of the things they think are happening actually are. With the vaccine that might mean you start by saying, 'Look, I realize that health care has turned into a massive moneymaking operation for those at the top, but this intervention can really help you and the people you love.' If you try to deny it and paint the health care system as a beautiful savior, people will think you're not taking them seriously and seeing what they see."

Trust in organized religion, government, public schools, and journalism has decreased significantly, with "the medical system" being one of the hardest-hit categories.

Telling patients that a large percentage of their neighbors are vaccinated, for example, can help to depoliticize the issue because, Van Bavel says, "people trust their personal doctor a lot, even though they may be on a weird corner of the internet where they're hearing that nobody gets the vaccine. Accurate numbers can nudge people toward the right behaviors."

So can supportive social networks. Dhand, Corbin, and their colleagues at HNI have been trying to change the model of care for patients recovering from a stroke by enlisting the influence of family and friends.

"In Western medicine disease is considered an individual biologic entity," says Dhand. "But it's well documented in animal and human models that interaction with other members of your species increases recovery and all kinds of biomarkers for health. Our idea is to take the focus off a patient's willpower and say, 'OK, Lucy, Matt, and Frank, you guys really care about your mom. Can you take her blood pressure daily? Eric, you're far away but can you find her a gym? Sally, you're the neighbor, we think you could get her to eat a healthier diet by bringing over a nonsalty meal once a week.'" This treatment model requires a fair amount of buy-in, Dhand concedes, but the rise of virtual meeting places has made the job easier, and early results have been encouraging.

"I'm often tempted to think bigger and to ask how we fix the system," says Corbin. "That's an important question. But for most of us, most of the time, the kind of power and leverage we have to do good work is on a local scale. As that adds up, it could eventually lead to big changes we can't even foresee today." HM

Elizabeth Gehrman is a Boston-based writer.

"People care a lot about social rewards. If they could gain status by being accurate, they'd be more likely to share based on that."



In 1799, while in Haiti to "secure his family's plantations," French national Michel Etienne Descourtilz was arrested and pressed into service as a physician under Jean-Jacques Dessalines, a leader in the rebellion that secured Haiti's independence. When not tending the wounded, Descourtilz collected plant specimens from the tropical forests in the area that now forms the border between Haiti and the Dominican Republic. That project supplied the material for his eight volumes on the natural history of the region's flora. In 1827, he published yet another taxonomic text, the *Atlas des champignons: comestibles, suspects et vénéneux*. The book contained this and other lithographs by artist A. Cornillon. *Champignons Suspects* features many of the mushroom species that we now know have psychedelic properties.



ATLAS DES CHAMPIGNONS: COMESTIBLES, SUSPECTS ET VÉNÉNEUX. M.E. DESCOURTILZ. 1827

Growing evidence for the safety and efficacy of psychedelics could lead to better treatments for anxiety, depression, pain, and other often intractable conditions

Altered Perceptions

BY ALLISON ECK

JERRY ROSENBAUM WAS INTRIGUED when he first heard about the effect that psilocybin—the hallucinogenic compound found in certain species of mushrooms—was purported to have on the brain's "resting state," what neuroscientists call the default mode network. Associated with daydreaming and thinking about the past or the future, the default mode network encompasses any neural function that has some bearing on our autobiographical tendencies.

"Given the nature of the results, I was eager to learn more," recalls Rosenbaum, the Stanley Cobb Professor of Psychiatry at HMS.

The information that grabbed Rosenbaum's attention was being delivered by Robin Carhart-Harris, a Hugh Grant-esque young Brit speaking remotely from the United Kingdom to participants at a 2018 conference on psychedelics at the Broad Institute in Cambridge, Massachusetts.

Carhart-Harris, a psychologist and head of the Centre for Psychedelic Research at Imperial College London, was describing recent neuroimaging research out of his lab demonstrating that when people take psilocybin at low doses, the default mode network becomes less active. That is, the drug appears to tame self-reflection and all but ruin rumination, that obsessive mental state characterized by excessive, repetitive thoughts.

"I often say that rumination is self-reflection gone awry," says Sharmin Ghaznavi, an HMS instructor in psychiatry and an attending psychiatrist at Massachusetts General Hospital. Rumination is a hallmark cognitive symptom of depression.

Last November, a pharmaceutical company announced promising, although not yet published, results from a clinical trial of psilocybin's effect on severe depression. The researchers found that nearly 30 percent of the participants given 25 milligrams of the compound were in remission three weeks after treatment, compared to less than 10 percent of those in the control group. The study's findings were generally considered encouraging by researchers in the field. At the time of its completion, it was the largest randomized, controlled, double-blind trial of psilocybin to have been conducted.

Ghaznavi and Rosenbaum are among those who see promise in the findings and note that they would be especially compelling if the drug being studied were a traditional antidepressant. But psychedelics research is in its early stages and the threshold for results being judged impressive is high. "There's so much we still have to learn," Ghaznavi says.

Anne St. Goar, MD '79, a researcher and psychedelic therapist, also attended Carhart-Harris's talk and remembers Rosenbaum's enthusiasm. They went out to dinner with a few peers afterward and batted around some ideas.

"Seeing evidence of decreased default mode network activity really piqued Jerry's curiosity," St. Goar says.

That dinner provided the initial spark for the Center for the Neuroscience of Psychedelics at Massachusetts General Hospital. Launched in early 2021, the center aims to assess how psychedelic substances could be used to improve the treatment of mental illnesses like depression, anxiety, substance abuse, eating disorders, phobias, obsessive-compulsive disorder, and post-traumatic stress disorder (PTSD).

"We really want to understand what is happening in the brain, from molecular to cellular to network and beyond," Rosenbaum says. "What happens that allows people to improve and recover? And what sustains that?"

A constellation of researchers as interconnected and electrified as the neural networks many of them study has emerged not just at Mass General but throughout the HMS ecosystem and beyond. With expertise in multiple fields—from palliative care to psychiatry to law—these experts have a dedicated interest in piecing together the ways psychedelic therapies could transform medicine imminently, and maybe permanently.

Rebirth of interest

Their efforts seem timely. With the counterculture movement of the '60s and '70s and the antidrug movement of the '80s receding into our collective past, the stigma associated with psychedelics has waned significantly. Scientists, mental health professionals, legislators, and the public at large are becoming increasingly fascinated by the possibility that psychedelics could alleviate some of the most extreme varieties of human psychological disease. Important studies, once frozen by the strictures placed on certain hallucinogens under the 1971 U.S. Controlled Substances Act, are being given a second life through philanthropically funded research initiatives at Yale, Johns Hopkins, and the University of California's San Diego and Berkeley campuses. In January, the National Institutes of Health hosted a groundbreaking, free virtual workshop on psychedelics as therapeutics for some 1,500 attendees.

A psychedelic renaissance is upon us from a commercial standpoint, too. According to one analysis, the market for psychedelics could be worth $7 billion by 2027. *JAMA* reported that as of January 2022, there were more than 50 publicly traded companies in this space, with at least three U.S. companies valued at more than $1 billion. And bills are being introduced in state legislatures across the country—from Washington and California to Pennsylvania and Maine—to legalize medical psilocybin, decriminalize it, or both.

With the antidrug movement of the '80s receding into our collective past, psychedelics' stigma has waned significantly.

Yet Stephen Haggarty, an HMS associate professor of neurology and scientific director of chemical neurobiology for the Mass General center, thinks something special is happening at Harvard.

"In the twenty-five years I've been at Harvard I haven't seen anything that has as much potential to connect the faculty of arts and sciences, the medical school, the divinity school, and even the law school," says Haggarty. "We have an amazing world-class community of investigators across the whole spectrum."

Out of the ashes

When it comes to psychedelics, though, Harvard also has a troubled past. The psychologist and psychedelic advocate Timothy Leary was a Harvard professor who, from 1960 to 1962, partnered with his colleague Richard Alpert (later known as Ram Dass) on the Harvard Psilocybin Project. Their efforts were methodologically, and ethically, ambiguous at best: Faculty members and administrators expressed alarm that the researchers often conducted their experiments while under the influence of psilocybin themselves, that they were sloppy in their research design, and that, in addition to using volunteer graduate students in their research, Alpert administered psilocybin to an undergraduate off campus. Harvard ultimately fired Leary and Alpert in 1963.

Haggarty wants to refocus the narrative. He recalls Richard Evans Schultes, a former Harvard professor, pioneering environmentalist, and scientist who researched medicinal plants in Mexico and the Amazon region and who is now known as the father of ethnobotany. Schultes started out as a scholarship student at Harvard College, initially interested in medicine. Yet his focus shifted after he took the class Plant and Human Affairs an experience that led to his spending a summer in Oklahoma with the Kiowa people studying the use of the cactus peyote, a source of mescaline. During a long career that included several positions at Harvard, Schultes formed ties with Indigenous knowledge-keepers, chemists, psychiatrists, and others in an attempt to elucidate the medicinal and cultural value of psychoactive plants.

"He laid a foundation of interdisciplinary science that we're trying to bring back to life," Haggarty says.

Franklin King, an HMS instructor in psychiatry and director of education and training at the Mass General center, says



"We really want to understand what is happening in the brain, from molecular to cellular to network and beyond. What happens that allows people to improve and recover?"



Sharmin Ghaznavi and Jerry Rosenbaum

JOHN SOARES

The primary reason psychedelic drugs trigger nonordinary states of consciousness is that they bind to a particular receptor in the brain.

that changing the narrative goes beyond just rethinking Harvard's history. It will also entail reflecting on the difference between treatment and healing, the definition of "cure," and the doctor-patient relationship.

"Most people who are really invested in this work have some kind of commitment to changing the paradigm underneath it," he says. He acknowledges, however, that it may be a long time before we can safely integrate hallucinogens into therapeutic practices.

King points out that psychedelic drugs have long been an accepted part of many of the world's cultures—and that recent adopters of psychedelic-assisted therapy must take care not to appropriate the strategies and assume they are immediately compatible. "Nonordinary states of consciousness have been integrated into communities in most civilizations other than the dominant civilization of the West for the past two millennia," King says. "That is not a commentary on whether these drugs will be safe or not safe in some future theoretical situation. We're a different culture."

Test and measure

Arguably one of the biggest factors in making psychedelic research more accepted in the United States and elsewhere is the knowledge that psychedelics produce no neurotoxic effects at the doses administered in clinical trials. In fact, neuroscientists are observing that, when taken in a controlled setting, these substances are beneficial to the brain, especially for people who have certain psychiatric disorders. Landmark studies in 2014 and 2016 showed that LSD and psilocybin alleviated existential anxiety in patients with life-threatening illnesses for up to a year after beginning the treatment. Other studies have shown that ketamine may strengthen neurons against the damage from chronic stress by preventing synapses from being flooded with glutamate, an amino acid that, in excess, withers dendrites. And researchers continue to investigate whether psychedelics are useful as anti-inflammatory agents.

In general, scientists seem to agree that the primary reason psychedelic drugs trigger nonordinary states of consciousness

is that they bind to a particular receptor in the brain, which promotes the release of serotonin, dopamine, oxytocin, and other chemical messengers into synapses. What experts don't understand is how these temporary experiences produce long-lasting, positive neural change.

"The deepest neuroscience question here is the basis of that persistence," Haggarty says. His lab is searching for clues about what happens after a psychedelic agent targets its receptor. If he and his colleagues can trace the resulting domino effect on the brain's circuitry and figure out which aspects help catalyze the therapeutic response, they could uncover new pharmacological strategies for more effectively targeting or circumventing the receptor altogether. Since psychedelics appear to reawaken the brain's neuroplastic potential, prompting a "childlike" state of openness and wonder, they are an enticing lens through which to explore more than psychiatric disease.

"It's all about the potential to make a broad impact by looking at basic mechanisms and transdiagnostic processes," Rosenbaum says.

To begin to characterize these basic mechanisms, Ghaznavi has initiated a Harvard-based human study involving psychedelics. It will use neuroimaging to analyze the effects of psilocybin on brain networks involved in rumination. Rosenbaum and Ghaznavi also hope a study by colleagues will move forward; it will investigate how MDMA (ecstasy), when paired with mindful self-compassion, influences symptoms of PTSD and feelings of loneliness among veterans with the treatment-resistant disorder.

Experts in the field are particularly excited about MDMA because so much work has been done on it. Within the next two years, scientists and advocates are likely to succeed in securing FDA approval of MDMA for clinical use. Such a milestone would be due in large part to the efforts of MAPS, the Multidisciplinary Association for Psychedelic Studies, founded in 1986.

St. Goar was a therapist for the first phase 3 trial, sponsored by MAPS, of the effects of MDMA-assisted psychotherapy for individuals with severe PTSD. Study participants, 90 percent of whom had previously contemplated suicide, engaged in three preparatory therapy sessions with two trained therapists, and then underwent three eight-hour sessions over the course of three months, during which they took MDMA or a placebo and talked with the same two therapists. Between MDMA sessions, the participants had weekly therapy, starting the day after each MDMA session and continuing for a few weeks after the last MDMA session. Overall, including the therapy, the treatment took four months.

MDMA may be especially helpful for treating severe PTSD over other disorders because it brings about feelings of emotional communion.

The results, published in *Nature Medicine* in May 2021, made headlines: Two months after treatment, 88 percent of participants with severe PTSD experienced a clinically significant reduction in PTSD diagnostic scores, compared to 60 percent of placebo participants. Additionally, 67 percent of participants who had received MDMA no longer qualified for a diagnosis of PTSD, compared with 32 percent in the placebo group.


Anne St. Goar

Positive findings from a second phase 3 trial, which is currently underway, could usher in further research into psilocybin, LSD, mescaline, ayahuasca, and other psychedelics.

"What we're going to see is an explosion of clinical trials done in other populations," Haggarty says. "What's been established is that the molecules are generally well tolerated and can be delivered safely, and that the clinical world is developing new paradigms to optimize such care."

Walk with me

The importance of the therapist's role in creating the right conditions, or what experts refer to as "set and setting," for psychiatric improvement cannot be overstated, St. Goar says. And because it differs from regular psychotherapy, it requires special training.

"Therapy is a crucial part of this," she says. "We're not talking about just giving patients the medicine and telling them to go home and take it. It's vital that the therapy is strong and supportive."

MDMA may be especially helpful for treating severe PTSD over other disorders because it brings about feelings of emotional communion: one study demonstrated that octopuses become more social when given MDMA. In a therapeutic setting, emotional communion often translates to patients with PTSD openly sharing their experiences, reliving their traumas by talking about them, and then feeling a surge of self-compassion that allows them to separate from their past and move forward. The therapist provides a safe setting and acts as a nonprescriptive guide throughout the therapeutic session.

"One of the issues right now is how to train enough therapists to do this work," St. Goar says. She recently worked with Janis Phelps, the director of the California Institute of Integral Studies, to create a Boston cohort for Phelps's training program. This year, 120 people from the Boston area completed the program. But St. Goar says that more must be done to build an infra-

structure for what many see as an inevitable wave of new medicinal approaches ahead.

"It's not the kind of training that leads to an automatic job," she says. "Right now, the only way you can administer these medicines legally is through a research protocol."

Yvan Beaussant, an HMS instructor in medicine and a palliative care physician at Dana-Farber Cancer Institute, is also trained in psychedelic-assisted therapy. He's been researching the effect of psychedelics on demoralization in patients with serious illnesses and has begun a pilot study to assess how psilocybin-assisted therapy could be integrated into serious-illness care. He says that it's critical to think about how to implement therapist training and certification programs into hospice care.

"The only way I heard about psychedelics in medical school was through classes about addiction and substance abuse," he says. "I hope that in medical, psychology, and chaplaincy curriculums there will be more opportunities for training."

Amanda Kim, a psychiatry resident at Brigham and Women's Hospital, runs an affinity group through the Boston Psychedelic Research Group that serves as a community for clinical trainees to share their perspectives on psychedelics and brainstorm ways to pursue their interest in this area.

"One thing we're trying to do is advocate for some type of training opportunity for psychedelic-assisted therapy that's accessible to clinical trainees," Kim says. "Although a few psychedelic training programs exist, they have limited capacity and can be expensive, making them out of reach for many clinical trainees. As these therapies become approved for clinical use, there is going to be a bottleneck of trained professionals who can deal with these powerful substances. Having more people, especially coming straight out of training, who are knowledgeable about psychedelics will be very important for the future."

In addition to the problem of how to scale therapist training, a number of infrastructural elements face practitioners who hope to someday roll out these medicines. For example, it remains to be seen how insurance companies would reimburse these treatments, and more research needs to be done on what specific therapeutic contexts are most helpful.

Alex Simon, an advisor to the Mass General psychedelics center, regularly organizes programs to help philanthropists, investors, and others become familiar with the current research around psychedelics. While his mission is to galvanize support for this work and identify structural barriers to its growth, he also wants to caution people against thinking that psychedelics are a silver bullet.

"This is a space that has extraordinary promise for helping a lot of people," Simon says. "I would encourage anyone involved to maintain enthusiasm but marry it with a level of rigor and sobriety that will mitigate the risk of disappointment or of overpromising."

A number of infrastructure elements face practitioners who hope to roll out these medicines. For example, it remains to be seen how insurance companies would reimburse these treatments.

Plans and possibilities

While Simon is working to understand the evolving psychedelics ecosystem, some researchers are probing other aspects of the use of psychedelics.

King is building education programs, and Haggarty is starting to examine the question of whether psychedelics can be a gateway to precision medicine. Specifically, he's inducing patient-derived pluripotent stem cells to become neurons and glia, then studying the resulting neural interactions in the lab to document neuroplasticity changes at the molecular, cellular, and circuit level. Someday, he says, the field might arrive at very precise predictions and descriptions of how each patient responds to different psychedelic drugs.

That's a positive step for neuroscience as a whole, according to Simon. "Using these compounds and healing modalities could open up a much larger arena of understanding the brain," he says.

Others grapple with how the economic model for psychedelic-assisted therapy will unfold and with issues related to inclusion.

"As psychedelic-assisted therapy becomes more of a reality, it's going to be very important to ensure there's equity of access," Kim says. "If research shows that these types of treatments can be helpful for everyone, they should be accessible to everyone."

Ensuring widespread availability means understanding that each patient comes to these drugs with a story. No matter their background, respecting a patient's individual experience during any such therapy session is paramount.

"One of the great potentials and risks of psychedelics is that they bring people into a space of greater vulnerability, self-discovery, and authenticity," says Beaussant. "This is the soul of psychedelic-assisted therapy, and we want it to be preserved. This is a human encounter that acknowledges the joys and difficulties of being human and requires the highest of ethical standards." HM

Allison Eck is the executive communications manager in the HMS Office of Communications and External Relations.

"Therapy is a crucial part of this. We're not talking about just giving patients the medicine and telling them to go home and take it. It's vital that the therapy is strong and supportive."



in 5

A conversation with Jun Huh, associate professor of immunology in the Blavatnik Institute at HMS

Why do you work on untangling how infection and inflammation affect immune system function and neurodevelopment?

We've made great progress in treating cancer and infectious diseases, but not in neurodevelopmental and neurodegenerative diseases. We need transformative techniques to develop treatments; I believe the immune system can help us achieve this. I think our immune system has evolved to stabilize or restore homeostatic balance when things go awry. It interacts with many organ systems. It can, for example, receive and process signals from the gut microbiota and affect the function of the nervous system. I anticipate that ten years from now "neuroimmunotherapy" will be used to treat Alzheimer's, Parkinson's, and even autism spectrum disorder.

What sparked your interest in this line of research?

Two things: a class I took as a PhD student and luck. One of my professors told us about research showing that pregnant women who get hospitalized with infections are more likely to give birth to children with autism. That made no sense at the time, but I remembered it. Later, I found a paper describing this phenomenon in pregnant mice, but it identified a signaling pathway and showed that cytokine IL-6 plays a role. I was then studying a class of IL-6-dependent T cells. I wanted to test the hypothesis that sociability deficits in offspring were related to the immune cells I was studying, but to do that I needed a neurobiologist to measure mouse behavior. And this is where good fortune entered: I married a woman who was doing postdoctoral work in neurobiology. It was a marriage of two fields before neuroimmunology was even a thing.

What do you hope to achieve as co-lead of the Fairbairn Family Lyme Disease Research Initiative?

My co-lead, Isaac Chiu, and I are trying to understand the neuroimmune connection in Lyme disease—why and how an infection with the bacterium that causes Lyme disease can lead to lingering long-term neurologic symptoms in some people. Without a clear mechanistic understanding of this process, we cannot design treatments. Our first step toward discovering such a mechanism is creating a good animal model.

What great challenge do scientists face today?

Funding. I have so many ideas I'd like to pursue. I'd love to do ten different experiments tomorrow, any of which could be potentially transformative. The funding challenge leads us to cast aside some exciting ideas. It's what keeps me up at night.

What or who inspires you?

I had a chance to present our data to parents of children with autism. Although our work is based on preclinical mouse models, these young mothers and fathers—some of whom had brought their children along—were so attentive and so focused on our work. I hope we can help them and, hopefully, within my lifetime. That humbles—and motivates—me. I have also been inspired by my best friend, who recently passed away from ALS. I am an immunologist at HMS, and I felt so helpless. The death led me to start work with ALS mouse models. Perhaps my lab will one day help us understand the causes and mechanisms of the disease.

—Ekaterina Pesheva

JOHN SOARES (THIS AND FACING PAGE)

Student Life



Elizabeth (Liz) Roux

NOTHING FOCUSES THE MIND like being attacked by a grizzly bear, and Liz Roux has been attacked by several, literally and metaphorically, in her 25 years on the planet.

Born in China, Roux spent her first year in an orphanage after being abandoned for reasons unknown. That metaphorical bear was vanquished by a U.S. woman who adopted Roux at 11 months old. The two made a happy family in Naples, Florida, until, when Roux was 15, her mother was diagnosed with the cancer that would take her life a little more than a year later. Roux says she felt lost after her mother's death, but she gradually grew closer to her high school running coach and his family, and considered herself "insanely lucky" when they unofficially adopted her. Around the same time, though, Roux's new younger brother, David, was diagnosed with a cancer that would prove fatal in just over two years. "At the time, I felt like a bad luck charm," Roux says, but even so, "all the talk about how love and family are the most important things really hit home."

It took a literal bear attack, though, to bring her fully back to the world of the living. She was leading a hike through the backcountry of Alaska when she got ahead of the group and surprised the animal. "It stood on its hind legs, grunted at me, then slammed down on all fours and charged," she recalls. She hit the ground, using her backpack as cover. The bear was tearing up the pack when the rest of her group came along and chased it off. "That moment really changed me," Roux says. "It made me appreciate life so much. I felt awe and humility for nature and a lot of vitality."

That experience, in part, led her to concentrate in integrative biology at Harvard, with an eye toward becoming a marine biologist. She began looking toward medicine instead after she realized that only about 10 percent of her time would be spent on field work. She chose HMS for two reasons: "the accelerated curriculum is perfect for someone who is yet undecided on a medical specialty," and her undergrad years showed that her fellow students at Harvard could help create an environment that "pushes me to become a better version of myself."

Serving as health and wellness chair on the student council is in keeping with Roux's habit of finding "chosen family" and creating community wherever she goes. She's interested in surgery and wilderness emergency medicine and imagines a future where she can practice in the mountain west, such as Utah or Colorado, while helping to run a community garden, volunteering at the local food pantry, and perhaps coaching the high school running or soccer team. "I always find things to be grateful for," she says. "Life is not perfect and it's not easy, but it is good."

—Elizabeth Gehrman



Yoseph Boku

WHEN YOSEPH BOKU LEFT HIS HOMETOWN of Addis Ababa and immigrated to Alexandria, Virginia, with his parents and six older siblings, he was only 6 years old, but he knew his job: to learn. "My dad went to school until eighth grade, and my mom didn't go at all," he says. "Educational opportunities were limited in the Ethiopian countryside where my parents were raised. Despite not having much formal schooling themselves, my parents brought us to the U.S. so that their children could pursue higher education."

His parents ended up returning home after less than a year, and his sister, who was 25 at the time, became Boku's legal guardian. "I was raised by my siblings with the support of the local Ethiopian community and my teachers," he says. "I felt like I was paying the highest tuition, which was separation from my parents. To ensure that our sacrifice wasn't in vain, I had to make sure I was learning."

Though he arrived in this country knowing no English, by third grade he was in the Fairfax County Advanced Academics Program. His hard work over the next decade paid off when he was accepted to Harvard College, where he concentrated in molecular and cellular biology. "My parents didn't know what Harvard was," he says. "When I tried to explain it to them, what ended up helping the most was when I told them that's where Obama went to school. Then they told all their friends."

He loved the puzzle-like nature of science and came by medicine naturally. Gastroesophageal reflux disease runs in his family and hit one brother particularly hard. "We didn't have health insurance, so I'd go to the emergency room with him and act as translator," Boku says. During a high school summer program on human genetics his assignment was to diagnose a hypothetical patient. "I felt so connected to that patient, even though she wasn't real," he says. "That's how I knew this was something I wanted to do for the rest of my life."

Another summer program, the American Legion Boys State, which teaches students about government, turned Boku on to policy and public service, but after volunteering at a homeless shelter in his first undergrad year and learning about health inequities, he says, "I realized it doesn't have to be science or social justice—it can be both."

He sees his role as student council president as presaging a career in advocacy, where he'd work at the intersection of "doing clinical research, seeing patients at the bedside, and advocating for the changes that would make our health care system more equitable," he says. "I would like to wake up each day with a sense of calling, knowing that my work is alleviating suffering."

—Elizabeth Gehrman



JOHN SOARES (THIS AND FACING PAGE)

Marium Raza

MARIUM RAZA WAS JUST 14 when she first realized "what it meant to be a doctor and help someone," she says. That was the year she was diagnosed with juvenile rheumatoid arthritis. Though her illness is now well controlled, "it was a very stressful time for me and my family, and not just anyone could talk with us the way my rheumatologist did to help."

That experience, along with her innate curiosity, led her to major in biochemistry at the University of Washington in her hometown of Seattle. "Being able to understand what was happening to me and why was one way to cope with my disease," she says. By her junior year of college, the idea of a career in medicine had solidified, thanks to two key occurrences. "From an early age I was aware of the health care inequities between the United States and Pakistan, where my parents grew up," she says, "but it wasn't until I volunteered for my school's street medical team that I saw inequities right here in the U.S." The second thing that drove this career idea home was her friendship with a student whose parents were undocumented. "I saw the vast difference between her family, who weren't eligible for the state's Medicaid system, and mine, where if something happened we could just go to a doctor."

After she started advocating for people who, for various reasons, are not being well served by the health care system, Raza created Elixir, an app that lists Washington state's free clinics and community centers. She considered taking the nonprofit that grew out of the app national, but decided she wanted to "learn and explore more." The app and the nonprofit are now run by another team of students.

Creating Elixir, though, brought her a new goal: to become a physician innovator. "I want to see what I can do on a systemic level," she says, pointing out that that's what brought her to "not just any medical school," but to Harvard. "There are a ton of people here who think like me, and the whole city is so focused on innovation."

One way she's gotten involved in that innovation is by running for student council, where she now serves as vice president for advocacy—not just for her fellow students, but for the surrounding community as well. "The experience has only increased my passion for making sure everyone's concerns are voiced and everyone's voices are heard," she says. "I think the role of advocacy is intimately intertwined with the role of physician."

—Elizabeth Gehrman

Good **Choices**

SPARKED BY THE ENCOURAGEMENT OF A HIGH SCHOOL BIOLOGY TEACHER, Judith Hochman aspired early on to become a research scientist. She pursued her first graduate degree at Harvard University, a master's degree from the program in cellular and developmental biology, because she says she had a "naive idea that I was going to make some incredible advance in molecular biology, maybe cure some kind of cancer."

During the second year of the program, however, Hochman realized that spending each working day with test tubes was not going to be enough. So Hochman sought a medical degree at HMS, a decision that ultimately led to her current roles: an endowed professor of cardiology and a senior associate dean for clinical sciences at the New York University Grossman School of Medicine.

Getting to where she is now did not happen by accident, says Hochman. She readily acknowledges her many HMS mentors, including cardiologist Lewis Dexter, MD '36, at the Peter Bent Brigham Hospital, and Eugene Braunwald, former chief of medicine at Brigham and Women's Hospital.

Female role models were scarce—until she did research under Bernadine Healy, MD '70, as a cardiology research fellow at Johns Hopkins School of Medicine.

Now, Hochman mentors others, a role she enjoys. "Mentoring is one of the most important things I do. When you mentor people, they mentor people, then they mentor people, and it has a huge exponential impact."

Of all her formative relationships, however, she says the most important is the one with her husband, Richard Fuchs, MD '76, clinical professor of cardiology at Weill Cornell Medicine.

Hochman characterizes her career as "a progression of taking on new things and giving other things up." She found that running a research lab, directing a cardiac intensive care unit, seeing clinical patients, running clinical research trials, and raising three sons meant she had to make choices. She gave up running her lab and clinical practice to concentrate in the other areas. This decision led to discoveries, publications, a leadership position initially in a small multicenter trial, and then progression through the ranks to running three large multicenter NIH-funded studies and other sponsored clinical trials in cardiology.

Hochman calls the rise of collaboration and team science "an absolute joy. Research is more complex than ever and so collaboration is the name of the game."

Reflecting on how she managed a high-powered career while raising her children, she says seeing them become wonderful adults is so rewarding and worth every difficulty. "And I couldn't have done it without an incredible partner in my husband." *—Susan Karcz*

Judith Hochman, MD '77 | Harold Snyder Family Professor of Cardiology | Senior Associate Dean for Clinical Sciences at New York University Grossman School of Medicine | Codirector, New York University-Langone Health Clinical and Translational Science Institute

Manual Updates

The past two years have deepened and strengthened the focus large health care systems have on improving the public's health **Interview by Ann Marie Menting**



Paul Ramsey



Peter Slavin

MATTIAS PALUDI; BOB HANDELMAN (FACING PAGE)

After more than two years of battling COVID surges, supply and staffing shortages, and spiking operational costs, hospital administrators are evaluating lessons learned and which pandemic-related changes will be retained. We talked about these and other topics with Paul Ramsey, MD '75, CEO of UW Medicine, executive vice president for medical affairs and dean of the University of Washington School of Medicine, and Peter Slavin, MD '84, an HMS professor of health care policy who was the president of Massachusetts General Hospital from 2003 through early 2021.

Our mission is to improve the health of the public, and a major part is the research that advances prevention, diagnosis, and treatment.

HMM: You each have said that referring to large health care systems as academic medical centers with a clinical, research, and education triple mission is an inaccurate description of your institutions, that the true mission is to improve the health of the public. Could you describe how population health became central to your institutions' mission statements?

Ramsey: In 1992, the University of Washington restructured the leadership of our medical school and hospitals to have a single leader for an integrated health system that includes the medical school, the hospitals, the clinics, and some other nonprofit organizations.

In 2000, the UW Medicine Board, which oversees UW Medicine, voted unanimously to endorse a single mission, to improve the health for the public—meaning to improve health for all people around the world. To advance that mission, we need integrated excellence in our clinical, research, and learning activities. A single leader and a clear mission: to improve health.

Slavin: For similar reasons, about fifteen years ago, I recommended to our board that we change our mission statement to explicitly recognize community health as being one of our four missions, arguably our first mission given the history of the institution. If indeed we are here to improve health—and 80 percent of health is driven by what happens in the community, not within our walls—then I think it's incumbent upon us to understand those forces and be engaged in doing something about them.

With this change, we created new structures within the hospital to buttress the community mission: a board subcommittee, an executive committee that our chief of medicine chairs, and a senior vice president, who is responsible for community and equity. Perhaps the more significant integration that's occurring has been happening across the system: the formation of the Mass General Brigham system. Each hospital composes the health system.

HMM: These priorities are large and require significant resources. How do you balance their needs?

Slavin: I don't see these missions in conflict with one another; they are synergistic and critical to improving health. But in terms of balancing, I think it comes down to how the economics of the institution work. Of those four areas of focus, only one of them—the clinical mission—generates a margin. The others absorb margin or require investments to sustain them. So that does require balancing. How do you generate enough margin from clinical activities or supplement it with things like philanthropy to be able to carry on robust activities in the other three mission-critical areas?

Ramsey: I agree. The clinical, research, and learning activities are synergistic and organizationally we should strive to integrate them in an efficient way that promotes synergy. Our mission is to improve the health of the public, and a major part of providing the best care for all people is the research that advances the knowledge for prevention, diagnosis, and treatment.

Because research is changing medicine so rapidly now, lifelong learning for the entire workforce is critical.

Some of the best learning for our students, even those students who go into a specialty career or research, comes from their experiencing the practice of medicine in a community that is so small and so remote that it often has one or two family physicians and then quite a bit of telehealth.

Our community-based teaching programs have included telehealth since the 1970s, and we have experienced a dramatic increase in digital health connections over the past two years, during the pandemic.

HMM: What other changes has the pandemic brought to your institutions?

Ramsey: I have nearly fifty years of time in medicine, and I have never, ever seen so much change and so much uncertainty as I have in the past two years. But I believe strongly that we can learn from the change and continue to make positive changes that are needed. For me, those changes fall in four areas.

I'll start with health care equity and diversity, equity, and inclusion. The pandemic has made us focus on the inequities related to COVID diagnosis, treatment, and prevention. The distribution of the vaccines enabled us to identify health care inequities and develop solutions. We have more work to do to achieve health care equity.

As I've mentioned, telehealth changed. In just the first two months of the pandemic, we moved ahead more than five years in the implementation of our telehealth strategic plan. Telehealth is transforming medicine and provides an opportunity to connect with patients in an efficient and timely manner.

Another area of pandemic-related progress has been value-based care efficiencies: the way we work and cost-effectiveness. This is important to an integrated health system that is heavily focused on advancing knowledge via research. I have never seen translational research move so fast—from basic science research to practical clinical application. This goes beyond the implementation of the COVID vaccines. We've accelerated translational research in many areas and are focusing on improving our internal infrastructure to continue to do that.

So many areas that were experiencing changes before the pandemic saw those changes accelerate during the pandemic to a breathtaking degree.

But one of the greatest challenges presented by the pandemic has been our workforce's well-being. Our staff, faculty, students, and residents have been working exceptionally hard and have had to move fast to meet changing circumstances. UW Medicine's offices of health care equity and faculty affairs support faculty and staff across all the sites and throughout the pandemic has focused on well-being, frequent and comprehensive communication, and resilience in the workplace.

I think if we build on these, we can really improve medicine and deliver better on our mission.

Slavin: That's a nice summary, Paul, of what we've both been experiencing during this pandemic.

I would start by saying that it has been for me both the best and the worst of times. Just seeing all the suffering of patients, many isolated from their families, was incredibly hard. What our caregivers have been through, after three waves of COVID, has been truly hard. I think for the first wave, adrenaline was at record levels. But that adrenaline wore off in subsequent waves. This pandemic has really been stressing our workforce.

So many areas that were experiencing changes before the pandemic have seen those changes accelerate throughout the pandemic to a breathtaking degree. I am on the board of a telemedicine company in Boston, so I've been especially aware of the activity in that area. Prior to the pandemic, I think less than 1 percent of our outpatient visits were conducted by telemedicine. At the peak of the pandemic, it was over 80 percent. I think it's now settling in around 20 percent or so, but the pandemic is teaching us that telemedicine is very feasible for a whole range of different clinical situations: it's more convenient for patients and it's more environmentally friendly because patients don't need to drive into the hospital or to a practice. The challenges that we face going forward include what the reimbursement for its use will ultimately be. Will it be economically viable?

Another issue raised by the pandemic and the use of telemedicine is state licensing of physicians and the inability of physicians to practice across state lines unless they're licensed in the other state. This has been a huge challenge. I think—I hope—that the attention raised by this problem will lead to national licensing of physicians. State-by-state licensing is a real barrier to progress.

We also have seen progress in how the whole research community has stepped up in an incredible way, pivoting to study COVID at the fundamental level and the clinical level.

At Mass General, we entered the pandemic with a robust clinical research program, but during the pandemic we built, almost overnight, an infrastructure that scanned the entire hospital for COVID patients. We made decisions about what trials to offer every patient and a very high percentage of COVID patients were enrolled in clinical trials. It was astounding.

Our systems also alerted us to the fact that our intensive care beds were being filled with patients from a relatively small number of communities, some of the lower-income communities that surround the hospital. So, we swung into action and met with the leaders in those communities to see what we could do to try to mitigate the disease and its spread in the communities. Our community health activities went on steroids. I don't know if we're going to be able to sustain the pace of change and innovation indefinitely, but I do hope we will sustain some of it. What happened was remarkable.

HMM: Each of you has mentioned the pressures placed on members of your workforce during the past two years. Could you describe what it has been like for your workforce and what you have been doing to counter these pressures?

Slavin: I think we did more of what we'd done previously, but there has not been one magic bullet for this problem. Part of the issue is the psychology of our workforce and the debilitating effects of the stress they have felt in what are challenging clinical situations. Adding to that stress is the fact that, particularly during the omicron surge,

a significant percentage of our workforce has been sick. We've had people leaving the profession because they've had enough, and we've had people who couldn't work because they were COVID-positive. This has caused huge staffing shortages that have only made things worse.

In terms of some of the things that we've done, I think one important thing is just leadership visibility. That's something that I've tried to do from the very beginning of my tenure, but I've stepped it up dramatically during the pandemic, as did other people in leadership, hospital trustees, and other senior leaders, who have been out there with our staff, showing them that what they were doing is incredibly important, listening to their concerns, and trying to do something about those concerns.

We also offered and continue to offer employee assistance programs for people who need help. Over the years, we've had an ongoing effort to identify ways to reduce physician burnout, from providing free opportunities to use a cycling place across the street to providing housing during the height of the pandemic—anything to show our workforce that we value them and to make their working environment as tolerable as possible.

Ramsey: Our workforce also has faced the combination of extremely hard, stressful work and longer hours in a setting of uncertainty and change. With surge after surge, we wonder, will this ever go away?

We have focused on enhancing communication not only for our workforce but for members of our regional community. At least weekly we had thousands of people participating in virtual town halls to discuss change. In these town halls, we listened to what was working, shared some best practices, and heard about specific challenges that we worked together to address. We've never had as much internal communication as we've had during the past two years. We also have been reaching out to local and regional communities to determine how we can better serve vulnerable populations.

We've also increased access to mental and behavioral health services, the need for which have only increased with the pandemic. Prior to the pandemic we hired someone to lead well-being at UW Medicine. She and her team have made a tremendous difference, including their creation of a large menu of activities so that individuals with different needs have different solutions available to them, ranging from exercise to childcare.

And engagement with community leaders has been important throughout this period. We have been working with them to better serve vulnerable populations. Fortunately many donors stepped up; in the first two months of the pandemic, we raised $30 million that we used for equity purposes, such as increasing COVID testing in these communities, providing vaccines, and producing information materials in multiple languages.

HMM: What sort of financial pressures have come with all this change?

Slavin: I think the strongest business pressure is the wage pressure for the workforce. The other things are relatively modest in comparison. One of the things that has put a lot of pressure on wages is the surge pricing charged by nursing agencies during the pandemic.

With traveling nurses doubling, tripling their rates, it creates difficulties within your organization. Staff nurses know that travelers are making twice what they are. That's not a formula for achieving stable wages or a stable workforce. And when you try to address the nursing wages, the domino effect occurs in other parts of the workforce, where people feel that they're underpaid and facing shortages. I left Mass General about six months ago, but my understanding is that the wage pressures have not abated.

Ramsey: The wage pressures for us were most severe in January 2022, but we expect ongoing challenges to our budgets due to increases in workforce expenses. I would add one thing to Peter's assessment: the current reimbursement system in general doesn't adjust to increases that are needed, such as increases in workforce expense.

When I speak with our first-year medical students I tell them that I envy them, that I wish I were starting medicine now.

The current reimbursement system doesn't recognize and incentivize programs that would make health care better and more affordable, especially for post-acute care settings, including home health care, which have been hit very hard. When we can't find a post-acute care setting in which patients can continue their care, we keep the patients in the hospital. That's a tremendous expense for the hospital system.

HMM: What makes you optimistic about medicine and health care as we look toward a post-pandemic period?

Slavin: I think the future of medicine is incredibly bright. There are obviously huge challenges, but I'm always inspired by the young people who are coming into the field and how bright they are and how committed they are to trying to help their fellow humans. I think the science of medicine has never been more exciting.

The changes ahead for the scientific basis of health care will transform every nook and cranny of medicine and of patient care in unimaginable ways. I think the other exciting megatrend that we're in the middle of is the digital health revolution. We've talked about telemedicine, but the effect that artificial intelligence, machine learning, and natural language processing will have on health care has just begun.

Ramsey: When I speak with our first-year medical students I tell them that I envy them, that I wish I were starting medicine now. We have the ability now to focus on health care equity, and we recognize it is mission-critical to advancing our goals for equity, diversity, and inclusion. We can measure population health and measure the outcomes of our care in ways that we couldn't before. This ability will help us achieve continuous improvement in health care and delivery. And then there's the accelerated application of what we're learning in the laboratories to improve health. That's so exciting. I think it is a wonderful time to start in medicine. HM

Ann Marie Menting is the editor of Harvard Medicine *magazine.*



During his work in Bogalusa, Louisiana, in the mid 1960s, Stanley Rapoport met several of the individuals who contributed significantly to the fight for the civil and voting rights of the city's Black community. This 1988 photo shows three of the people involved in that effort— Robert Hicks (left), A.Z. Young (center), and Gayle Jenkins (right)—in the abandoned Popkin Elementary School. Many of the all-Black segregated schools were closed after Bogalusa fully integrated its schools in 1969.



CHUCK COOK/THE TIMES PICAYUNE/1988/CAPITAL CITY PRESS/BATON ROUGE, LA

A Radical Turn

A physician recalls the fight to achieve equitable medical care for the Black community in one small town in Louisiana

by Stanley Rapoport

A GARDEN PARTY IN WASHINGTON, DC, was not a venue I would have thought would lead to my becoming radicalized and deeply involved with a small group of southern Black men and women seeking their civil rights. Yet, it was the first step on a road to precisely that.

In the summer of 1964, my wife, Judy, and I attended such a party. As we mingled with the other local health professionals, we learned about a group of doctors and nurses, members of the Medical Committee for Human Rights (MCHR), that was providing medical care for student volunteers in Jackson, Mississippi, who were registering Black voters. The MCHR had been founded in 1963 by medical luminaries from New York and Boston, some of whom I had met while a medical student at HMS.

In 1965, the MCHR wished to identify and rectify health disparities in the state of Louisiana. I volunteered to help with this. By March of that year, I had procured travel orders from the somewhat hesitant director at the NIH, where I was a Public Health Service (PHS) officer doing research. I was approved to go to Bogalusa, a small town in northeast Louisiana tucked near the border with Mississippi, to survey hospitals and available race-related statistics, conduct interviews, and produce a survey report that would help the MCHR prepare for the deployment it was planning in Louisiana for later that year.

In my third year at HMS, I had taken a public health course in which I surveyed Trenton, New Jersey. I evaluated health delivery resources provided by the private sector, the city, the state, and the federal government. I also analyzed published health statistics and racial disparities, visited hospitals and clinics, and interviewed doctors, nurses, health administrators, and patients. My supervisor at HMS, Joseph Stokes, MD '49, a cardiologist and epidemiologist at Massachusetts General Hospital and a founder of the MCHR, had approved my report and even suggested that I consider going into public health.

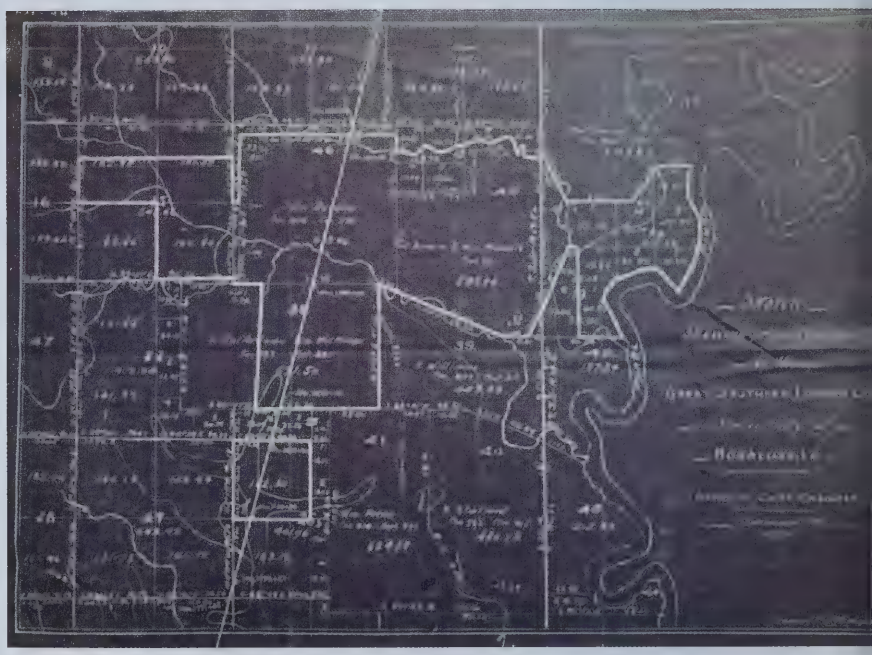
Riding shotgun

To prepare for my work in Louisiana, I reviewed health statistics for the state while also reading disturbing news of civil rights protests and their violent suppression in Bogalusa and elsewhere in the South. Nevertheless, I remained committed to my decision to go.

Race-based atrocities in the region were many. In 1964, three young civil rights workers had been killed by the Ku Klux Klan in Philadelphia, Mississippi, about 150 miles northeast of Bogalusa. In February 1965, a civil rights organizer from the Congress of Racial Equality (CORE) was severely beaten in Bogalusa by the Klan. One month later, in Selma, Alabama, Black and white protesters were beaten by police during a nonviolent march; one person was killed and many were injured, including John Lewis, a young Black activist and later a member of the U.S. House of Representatives.







Voter registration efforts in Bogalusa were burgeoning; CORE and the Bogalusa Civic and Voters League, organized by members of the Black community, announced that volunteers would be coming to the city and that, in early April, the CORE director, James Farmer, would lead a protest march targeting segregated lunch counters and other facilities. The Black community in Bogalusa mobilized; in early 1965 it formed the Deacons for Defense and Justice, an armed defense group dedicated to protecting the community and civil rights demonstrators from the Klan and the police, many of whom were themselves members of the Klan.

This was the environment I entered on the evening of March 30, 1965, when I landed at the New Orleans airport. As the plane touched down, I could almost hear the warning of the NIH director: "Whatever you do, Stanley, do not get involved in any civil rights disturbance, and do not mention that you are from the NIH or are a PHS officer. That could get us all in trouble." I had readily and, it turned out, naively, agreed.

I was met at the baggage claim by Joel Rubenstein, who introduced himself as a Bogalusa CORE representative. We climbed into his car and headed not north for Bogalusa, but south toward CORE headquarters on Dryades Street in the Black quarter of New Orleans. There, I reviewed my plans for my next few days in Bogalusa with the southern director of CORE. With his help, I identified people that I should meet and places I intended to survey. I especially wanted to visit the Washington-St. Tammany Charity Hospital, an institution built in 1951 with Federal Hill-Burton funds and subject to the Title VI desegregation requirements in the recently passed Voting Rights Act. When I finished discussing my plans, Joel told me that while in Bogalusa I would be the guest of the Hicks family.

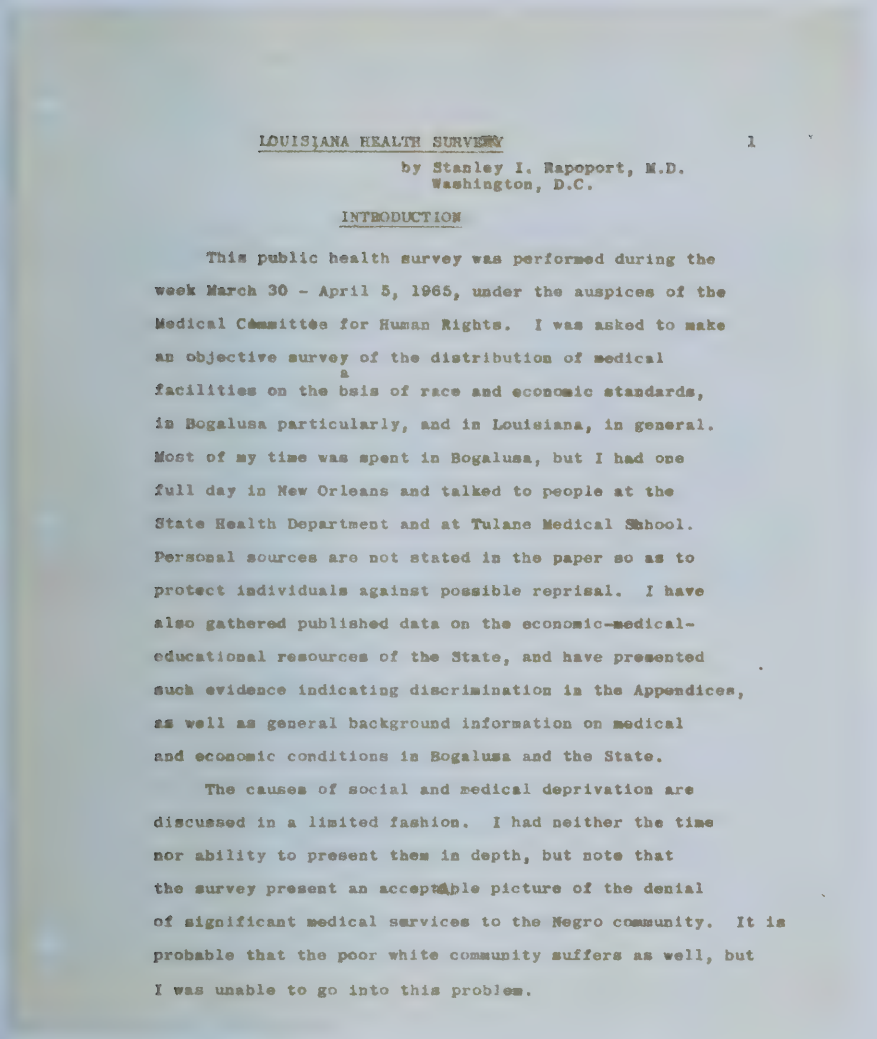
The Black community in Bogalusa formed the Deacons for Defense and Justice, an armed defense group to protect the community from the Klan.

Joel and I were headed north for Bogalusa by 10 p.m. Before putting the car in gear, Joel removed a black oiled revolver from his briefcase and placed it between our seats. "What the hell are we doing with a gun?" I asked him. "Well," he said, "as long as it's not concealed, it's legal in Louisiana. There's the Klan out there."

Far from equal

We drove along the Causeway, a 23 mile-long concrete highway above Lake Pontchartrain. At a sign announcing Mandeville, the Causeway diverged into a narrow, soggy road. After about 30

BARBARA SOBOL/LOUISIANA DIGITAL LIBRARY (LDL) (LEFT); THE ROBERT "BOB" HICKS FOUNDATION/DR. STANLEY RAPOPORT COLLECTION/LDL (TOP RIGHT)



LOUISIANA HEALTH SURVEY 1

by Stanley I. Rapoport, M.D.
Washington, D.C.

INTRODUCTION

This public health survey was performed during the week March 30 - April 5, 1965, under the auspices of the Medical Committee for Human Rights. I was asked to make an objective survey of the distribution of medical facilities on the bsis of race and economic standards, in Bogalusa particularly, and in Louisiana, in general. Most of my time was spent in Bogalusa, but I had one full day in New Orleans and talked to people at the State Health Department and at Tulane Medical School. Personal sources are not stated in the paper so as to protect individuals against possible reprisal. I have also gathered published data on the economic-medical-educational resources of the State, and have presented such evidence indicating discrimination in the Appendices, as well as general background information on medical and economic conditions in Bogalusa and the State.

The causes of social and medical deprivation are discussed in a limited fashion. I had neither the time nor ability to present them in depth, but note that the survey present an acceptable picture of the denial of significant medical services to the Negro community. It is probable that the poor white community suffers as well, but I was unable to go into this problem.

"The schedule of the outpatient clinic was different for 'colored' than for whites, with white patients having access in the morning and Black patients in the afternoon—if all whites had been seen."

minutes, our car quietly entered a barely lit agglomeration of houses. This was Bogalusa. We crossed a bridge to reach the home of Robert (Bob) and Valeira (Jackie) Hicks. Nervous Black men carrying shotguns surrounded me as I stepped out of the car. I became aware of a sulfurous stench in the air—the unhealthy effluent from the distant chimneys of the Crown Zellerbach paper mill.

I was greeted at the opened door by Jackie, a slight woman who grabbed my battered valise and tugged me into the darkened room where her husband was standing. She told me not to walk in front of a window and to keep the lights dimmed in the house at night, to avoid being a target. A shotgun leaned against a wall.

Jackie offered me a sandwich and a glass of milk, and we talked of my plans for the next few days. Bob told me that he had just been elected vice-president of the League and that I would soon meet A.Z. Young, the League's new president and owner of a small fleet of taxicabs that served the Black community. Both men worked at the paper mill and belonged to its long-established Black union. Later, Jackie showed me to what was evidently a young boys' room where I would spend the night. Her sons Greg and Rob were staying with A.Z.

Robert "Bob" Hicks stands in front of the CORE office in this mid 1960s photo (far left, facing page). A 1965 photo showing the Crown Zellerbach paper mill in Bogalusa (upper right, facing page). A map showing Bogalusa, Louisiana, and vicinity in 1906 (lower right, facing page). The opening page of the report (above) that Stanley Rapoport produced following his work in Bogalusa.

In the morning, an armed man, a Deacon, drove me to St. Matthews Episcopal Church to meet with its pastor. I reviewed with him the names of the people I planned to interview in the white community. He identified some who would be sympathetic and some who would not. He gave me his phone number in case of an emergency.

I went ahead with my business that day, walked into various offices where I had made appointments. At the end of the day, I called one of A.Z.'s taxis so that I could return to the Hickses' for dinner. After dinner, a Deacon came by and took me back into town for an appointment with the director of the community medical center.

"I'm very willing to discontinue segregation," the director told me, "if I were not forced to bear total responsibility for doing it."

The following day, I was driven to my appointment with the superintendent at the Charity hospital. He seemed nonplussed when I introduced myself, showed him my PHS identity card, and asked permission to survey the wards and waiting rooms. I told him I was there to determine Charity's compliance with Title VI. He angrily questioned my credentials, then called for a guard to escort me out of the hospital.

STATE ARCHIVES LOUISIANA DIGITAL LIBRARY (TOP); LOWER RIGHT, FACING PAGE); THE ROBERT "BOB" HICKS FOUNDATION/DR. STANLEY RAPOPORT COLLECTION/LDL













When I told Bob over dinner that evening that it was critical for me to survey the Charity, he said that he would arrange for me to return accompanied by a Deacon.

The next day, I interviewed Black men and women at A.Z.'s taxi service. We talked about their experiences at the Charity and about their health care issues. I learned that the doctors and nurses at the hospital treated Black patients with disdain. The schedule of the outpatient clinic was different for "colored" than for whites, with white patients having access in the morning and Black patients in the afternoon—if all whites had been seen.

One young woman told me, "When I was pregnant, they didn't offer me any predelivery care, so I lost my child at the last moment in the waiting room." I had read that neonatal and maternal mortality in the state of Louisiana was two times more common for Black patients than for white patients, worse than in any other U.S. state. Black people also had a 10 percent shorter life expectancy than did white people in Louisiana.

Later that day, my assigned Deacon arrived to take me again to the Charity. On its first floor, the benches in the waiting room were obviously segregated. On the second floor were two large pavilions for women. My Deacon companion identified faded spaces above the entrances, from which racial designations had been removed recently.

Images Stanley Rapoport captured during his work in Bogalusa include (top row, left to right) the Bogalusa Community Medical Center, children playing in front of mill houses, people gathering at the Hickses' home (also facing page), Bogalusa police monitoring the Hickses' home, and scenes from the first major civil rights march in Bogalusa, led by James Farmer, director of CORE, in April 1965 (second row, above).

One pavilion seemed cavernous; its surfaces were covered with peeling olive paint. It was filled with Black women lying in beds arranged in parallel as if in a sardine can. An aroma of urine permeated the air. A nurse's assistant sat at a table reading the *Bogalusa Daily News*, ignoring complaints.

The other ward, however, was less crowded. Its walls had been recently painted and its air conditioning was working well enough. White women in hospital garb lay in beds, their heads on plump pillows. An attendant went from bed to bed filling glasses with cold water.

I climbed the stairs to the second floor, where the two men's wards were located. The racial distinctions between the two wings on the first floor held for the second. The conditions in those wards, especially those where there were only Black patients, reminded me of what I had witnessed during my medical internship at New York City's Bellevue Hospital, full of coughs and the smell of suffering.

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M2224

** Recent grads can join the Dean's Council with annual gifts totaling $250 (1–4 years out from graduation), $500 (5–9 years out), or $1,000 (10–14 years out).*

DO NOT WRITE BELOW THIS LINE



THE ROBERT "BOB" HICKS FOUNDATION/DR. STANLEY RAPOPORT COLLECTION/LOUISIANA DIGITAL LIBRARY (THIS AND FACING PAGE)

Blue notes

I had been in Bogalusa for five days, visiting, gathering information and documents, and taking photographs, when I told everyone that I had finished my survey and wanted to leave soon. A few members of the Deacons, including Bob and A.Z., invited me to have a parting beer with them at the Blue Room Tavern in the Black center of town. It was April 4.

I was happy to accept. We had become comfortable with each other—and I had become entirely converted to their cause. I was sipping my second beer when the blue lights of a squad car came through the open door. Two policemen entered the bar; one ordered me to stand up, marched me out the door, and frisked me under the fluorescent glare of the bar's sign. He pushed me into the back of the squad car with Dolores, who had served me, and we were taken to the station.

At the booking desk, the officer glared at me and said, "Dolores served you in a bar that is only for n-----s. You are arrested as a material witness against her." It turned out that when Dolores served a white man—me—a beer, she had violated city and state ordinances that prohibited individuals of different races from drinking alcohol together.

When Dolores served me a beer, she had violated city and state ordinances prohibiting different races from drinking alcohol together.

"Maybe you want a lawyer," the detective in the police station said before tossing me a city directory and handing me the telephone. I called lawyers listed in the directory and explained my plight. None would help.

An officer pushed me into a holding cell, which held three bedraggled white men and smelled of urine and alcoholic sweat. At about 2 a.m., a policeman opened the cell and said, "You can leave, someone's paid your bail."

As I walked out of the station and into the town square, I noticed two dark sedans with Mississippi license plates, filled with white men puffing glowing cigarettes. I had an idea who those men might be—the Klan—so I stepped back into the station and told the officer that I needed to call a taxi. I called Bob and within ten minutes three cars filled with armed Deacons arrived and picked me up. Our cars rushed through the unlit streets followed by the sedans; shots were fired. The Deacon who was in the back seat with me pushed me to the floor.

Jackie was out of town that evening, so I was driven to the home of another Black family with ties to the Deacons. There I learned why



This photo, circa 1965, shows Stanley Rapoport (left) with Robert Hicks during the time Hicks was vice-president of the Bogalusa Civic and Voters League.

I had been released: after my arrest, one of my drinking partners had called the white owner of the Blue Room Tavern and told him to bail me out. Otherwise, the Deacons would burn down the bar.

At the Hickses' home the following evening, I received a call from a lawyer in New Orleans whose firm often represented civil rights workers. CORE and the MCHR had asked him to represent me. He assured me that he would arrange for me to leave Bogalusa and avoid appearing in court, but that it would take some time.

Solidarity

On the morning of April 8, the day slated for the protest march in which CORE's Farmer was to participate, everybody assembled at the Ebenezer Baptist Church. We sang religious and civil rights songs and ended by holding hands while singing "We Shall Overcome." The minister gave an encouraging sermon, then asked me up to the pulpit. I presented an emotional summary of the failing and discriminatory health care in the city, told all that their cause was just, and said I was honored to be with them in their quest for liberty.

On Sunday, April 11, eight days after my arrest, the city attorney telephoned to say that he had dropped charges against me. I was free to leave Bogalusa. I learned later from a court filing that the city attorney was an Exalted Cyclops of the local Klan klavern.

The next morning, Bob drove me back to New Orleans where I interviewed a physician at the state health department to learn more about the department's activities and about health statistics in Louisiana. I flew to Washington, DC, the following day, and began assembling data and notes for my report to the MCHR.

The MCHR used my report to mount a comprehensive campaign in 1965 to address the consequences of racial discrimination on health care in the state of Louisiana. In August, the executive director of the organization wrote to me saying that my paper, now recognized as the Rapoport Study, was going to be used by all the MCHR volunteers who left for Louisiana in the summer.

After I left Bogalusa, the NAACP sued the Charity in federal court, and won. Indeed, by early 1966, all public hospitals in Louisiana had been desegregated, as had nonpublic health facilities that received federal reimbursement funds under the newly passed Social Security Medicare Act.

From our lips

In 1967, A.Z. and Bob flew to Washington to testify in a desegregation labor dispute with Crown Zellerbach. Both visited Judy and me at our home.

After they returned to Bogalusa, I never saw them again. Their contributions to civil rights and racial equality were unyielding and glorious. They have passed away, as have so many others whose work was critical to the civil rights movement in Bogalusa and across the South.

Today, in Bogalusa, the Hicks house in which I stayed is listed for significance on the National Register of Historic Places and is slated to become a civil rights museum; historical documents from that time are being assembled in a digital collection for the museum. Photographs that I took while in Bogalusa, my associated documents, and my medical report and related correspondence from CORE and the MCHR will be part of a museum exhibition and are available now on the Louisiana Digital Library website. I am on the board of directors of the planned museum.

One Sunday morning each month, I participate in a prayer circle with Jackie and the extended Hicks family on a common telephone line. We celebrate the progress that was made in removing segregation and attaining equal rights for the Black community in Bogalusa, but also focus on what remains to be done to achieve racial equality and equity in our country.

Stanley Rapoport, MD '59, is a retired researcher who spent much of his career in the intramural program at the NIH. He resides in Washington, DC, with his wife, Judith, also MD '59.

PHOTOGRAPH BY ANNE MEUER/RONNIE MOORE PAPERS/AMISTAD RESEARCH CENTER/NEW ORLEANS, LA



The renovation of the Francis A. Countway Library of Medicine, which took place between 2019 and 2021, kept the sweeping stairs to the upper and lower levels and added an entrance onto Huntington Avenue.

STEVE LIPOFSKY

DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

When you were a student at HMS, **what were your favorite places to study, and why?**



In this 2018 photo, students work in the Student Study and Collaboration Center in the Tosteson Medical Education Center.



A view of one of the lounge areas in the Student Study and Collaboration Center in TMEC.

BETHENY VERSOY (THIS AND FACING PAGE)

Marguerite Barnett, MD '79

I would study any place that was warm. I could not afford heat in my tenement apartment behind Kendall Square in Cambridge.

Paul Shellito, MD '77

I would go to the Countway Library. It was close to Vanderbilt Hall, quiet, and cool looking, both inside and out.

Tamara Fountain, MD '88

Most of the time, I studied in my room; I lived in Vandy my first year and off campus the other three years. One of the few times I stayed at the Countway to study and then took the E-line trolley home, I was jumped on the short walk from the station and held up at knifepoint. He took my satchel and was probably pretty angry when all he netted were USMLE notes and a credit for Jordan Marsh (never rob a poor graduate student). Thankfully he let me go. He was caught by the Boston Police Department and let off with community service since it was his first offense.

Albert Levin, MD '60

I lived in Vanderbilt Hall during my first two years at HMS. My favorite venue for studying in the evening and on weekends was a small library on the second floor of the original rotunda building of Children's Hospital. For some reason, it was apparently unknown to other students. It was quiet and had an elegant atmosphere.

William Goodson III, MD '71

I would study in the basement of the Countway Library. It was quiet and had few distractions.

Victor Piotrowski, MD '74

I studied in the Hilles Library at Radcliffe College. I liked being among a more diverse undergraduate student body and social atmosphere.

James Reiss, MD '62

I would go to the Harvard University Faculty Club and the Widener Library. I was fortunate to have a Widener stack pass during most of my undergraduate and HMS years, and Widener was a quiet place to study—or to read old *Life* magazines and pulpers.

James MacDonald, MD '96

I lived off campus in Central Square in Cambridge. I enjoyed commuting by bike to and from home and Avenue Louis Pasteur. I always enjoyed studying at Widener Library, in part because I lived off campus, in part because I was slightly older (28) when I entered HMS, and in part because I am a graduate of the College ('85). Widener's atmosphere was far different from what could be characterized as the nervous energy of HMS.

Eubee Koo, MD '15

I loved the privacy of the tutorial rooms in Tosteson Medical Education Center. I'd put up a picture of a beach, put some tunes on, and study for hours on end, sometimes using the chalkboards to work through some thoughts. Sometimes I'd migrate to the atrium with its incandescent glow or creep through the underground tunnels to Shattuck for some late-night tea or coffee. I remember a few late nights drinking coffee (or, rarely, beer!) while doing question banks in those eerily quiet spots. Will never forget those moments!

Stephen Grund, MD '91

I was married with three young children so I studied whenever and wherever I could find the space, time, and quiet. Not easy. My wife helped me get through it. She's a saint. I owe EVERYTHING to her.

Robert Colvin, MD '68

I would go to the reserve book room at MIT. It was always open and was great for studying for second-year boards. My other study spot was the Countway Library.

Nneka (Azikiwe) Holder, MD '97

I would study in my dorm room and later on, off campus. Honestly, it was easier to study as a group with classmates **Abimbola (Abby) Aina-Mumuney, Charlene Brown, MD '98, Nadia Hansel**, and **Michelle Lee, MD '21**.



The renovation of the Countway Library included areas for study and collaboration such as this one on the first floor of the building.

STEVE LIPOFSKY

Ernesto Parra, MD '82

My two classmates and I would study late into the night on the top floor of Building A overlooking the quadrangle. Peering out the open window we could enjoy the smells, sights, and sounds of the beautiful Boston summer nights. There was the faint aroma of the sea, the bright colorful Citgo sign with nearby Fenway Park aglow, and the occasional distant roar of the crowd from the ballpark.

Mitchell Rabkin, MD '55

Now long gone, I suspect, but during my student years, in the dome of the Children's Hospital building on Longwood Avenue there was a quiet, comfortable place to go over the needed books, from *Gray's Anatomy* to the Cecil-Loeb *Textbook of Medicine*. In those days, one thought (at least partially) that if you could remember most of the contents of these basic textbooks, one might have a passable knowledge of medicine and its basic sciences. Such hubris disappeared; my first postgraduate year began a lifelong career of learning.

Richard Peinert, MD '73

I studied in the carrels at the Countway Library. The isolation was just great for a power grind.

Alan Baker, MD '66

The deafening quiet at the Countway Library made for absolutely unperturbed sleep.

Michael Quiñones, MD '86

I would go to the Harvard Business School library. The great hall's appearance was inspiring, and the quietude was calming.

Jan Polissar, MD '61

I would study in my Vanderbilt dorm room, where my most useful books were at hand.

Thanks to all who shared recollections of your favorite places to study while at HMS.

Please look online for these responses and those you have shared for the question ***How have the public conversations on systemic racism and implicit bias affected how you interact with patients and colleagues?***

Two new questions are coming your way! ***What book has had a profound influence on you, professionally or otherwise? Why and how?*** *and* ***How would you most like others to remember you as a physician?*** *Responses for these will appear online in summer 2022 and autumn 2022, respectively. The autumn 2022 responses will also appear in the print issue.*

Responses can be submitted online: ***hms.harvard.edu/rounds****; via email:* ***hmsalum@hms.harvard.edu****; by phone: 617-384-8520; or by mail: Rounds, Alumni Affairs and Development, Harvard Medical School, 401 Park Drive, Suite 505, Boston, MA 02215.*

Obituaries

1940s

1946

Philip H. Henneman, MD
February 27, 2021

Robert T. Strang, MD
November 3, 2020

1947

Warren C. Baldwin, MD
January 5, 2022

1948

Joseph M. Merrill, MD
June 27, 2021

Thomas N. Roberts, MD
August 15, 2021

Albert A. Simkus, MD
October 14, 2021

Clement P. Stodder, MD
January 31, 2021

1950s

1950

Arnold A. Lear, MD
December 4, 2018

1951

Michael Angelo Gravallese, MD
August 26, 2021

Richard A. Mayo, MD
September 23, 2021

William F. Simpson, MD
June 7, 2014

1952

Robert B. Berg, MD
February 5, 2020

William D. Cochran, MD
October 8, 2021

James F. Donovan, MD
July 26, 2021

Robert P. Fornshell, MD
February 10, 2022

Roy R. Grinker Jr., MD
January 8, 2022

Leo Samelson, MD
January 4, 2022

Vaughn R. Sturtevant, MD
October 10, 2021

Ben Taber, MD
December 25, 2021

1953

Iolanda E. Low, MD
December 25, 2021

1954

Arthur J. Garceau, MD
October 10, 2021

Edward Landau, MD
September 23, 2021

Alexander M. McPhedran, MD
December 17, 2021

1955

George E. Cobb, MD
September 21, 2021

V. C. Forbes, MD
August 22, 2021

Thomas E. Thompson, PhD
November 16, 2021

Thomas A. Waldmann, MD
September 25, 2021

1956

LeBaron W. Dennis, MD
December 24, 2021

John J. Spillane, MD
January 13, 2022

1957

Henry D. Onken, MD
November 1, 2021

George V. Smith, MD
December 18, 2021

Richard J. Wagman, MD
August 26, 2021

1958

Elizabeth E. Killoran, MD
January 27, 2021

Walter E. Nance, MD
October 17, 2021

Vernon D. Patch, MD
January 20, 2020

1960s

1960

Naomi B. Heller, MD
September 21, 2021

David G. Kamper, MD
September 8, 2021

Richard Kelley, MD
February 24, 2022

Robert Kleiger, MD
January 21, 2022

1961

Herbert Benson, MD
February 3, 2022

F. Curtis Dohan Jr., MD
November 16, 2021

Ralph E. Miller Jr., MD
November 21, 2021

1962

Robert L. Waldron II, MD
November 13, 2021

1963

Larry Matthews, MD
November 27, 2021

1964

Gary H. Manchester, MD
August 24, 2021

1965

Margaret Griffith Ward, PhD
August 7, 2021

1966

Stephen M. Brown, MD
October 31, 2020

Douglas D. Payne, MD
January 6, 2022

1967

Neil H. Joseph, MD
July 8, 2020

William M. Murphy, MD
September 1, 2021

Douglas G. Smith, MD
October 7, 2021

1968

Alexander M. McBean, MD
November 2, 2021

1969

Robert T. Graybeal, MD
September 22, 2021

David Hodes, MD
November 9, 2020

1970s

1970

Glenn W. Sandberg, MD
November 13, 2021

Michael B. Simson, MD
September 14, 2021

1971

Barry R. Fernbach, MD
August 14, 2021

John B. Hughes, MD
August 21, 2021

1974

William R. Whalen, MD
August 23, 2021

1976

Barry H. Brooks, MD
November 23, 2021

1978

Eileen Storey, MD
September 26, 2021

1980s

1981

Michael Thomas Crow, PhD
December 3, 2019

1982

Raymond D. Dickson, MD
October 17, 1992

1988

Gregory J. Spangler, MD PhD
November 27, 2021

1990s

1990

Paul E. Farmer, MD PhD
February 21, 2022

1996

Erich C. Strauss, MD
November 26, 2020

1999

Kristen Margery Upchurch, MD
May 29, 2020

This listing of deceased alumni includes those whose notices of death were received between September 1, 2021, and February 28, 2022.

PRESIDENT'S REPORT

Our Continued **Commitment to Excellence**



ALTHOUGH THE CONTINUING SOCIAL DISRUPTION CAUSED by the COVID pandemic required that the winter meeting of the Harvard Medical Alumni Council be held virtually, the discussions by members of the Council showed that HMS alumni remain united in their strong commitment to a student experience of uncompromising excellence. Dean George Q. Daley, MD '91, outlined the School's efforts to maintain students' invaluable in-person learning outside the clinics even as they staff the health care frontlines and support a strained patient care infrastructure during their hospital training.

The report on alumni financial donations indicated they remain robust by all metrics. In fact, the upward trajectory of MD alumni giving through the second quarter of FY22 was steeper than that seen during the past two years, a rousing endorsement at a critical time from those of us who benefited from an HMS education. Importantly, the Dean's REACH Scholarship Award Program continues to support a select group of incoming MD students by providing need-based four-year scholarships that help ensure their enriching presence in the student body.

HMS continues its commitment to an ethnically and racially diverse student body. Alumni support for this goal is shown by the enthusiastic embrace of the Alumni Council Recruitment and Mentorship Project, which was launched last fall. This project aims to bolstering recruitment to HMS of students underrepresented in medicine. The effort is a cooperative venture with the Office of Recruitment and Multicultural Affairs, headed by Andrea Reid, MD '88, HMS associate dean for student and multicultural affairs.

The program provides medical school applicants with alumni perspectives that supplement information from current HMS faculty and students. The rapid and robust response to an email request for alumni help in mentorship and recruitment showed broad interest across gender, ethnicity, and pentads. Nearly one-third of respondents were the first in their family to pursue medicine while 6 percent identified as being part of the LGBTQ community. Although 45 percent of respondents were from the Northeast, the West and South each rang up 21 percent. The breadth of alumni background provides applicants with an important lens into the richness one experiences as a member of the HMS family. The fact that alumni participants represented more than thirty-one specialties further cements the value of the program.

This program is one step in a broader effort to encourage alumni engagement with students during three key stages of their HMS experience: as applicants, matriculating students, and recent graduates. The aim over the coming year is to examine ways in which alumni can enrich the experiences of the latter two groups by learning from and partnering with existing support programs.

We look forward to seeing as many alumni as possible at the 2022 Reunion and Alumni Day events. The exciting program will include the presentation of the HMS Alumni Distinguished Service Award to DeWayne Pursley, MD '83 (Class of 1982), and should not be missed!

Kenneth Bridges, MD '76, is vice president of medical affairs for Global Blood Therapeutics, Inc., in San Francisco.

Alumni Announcements

MD Volunteer Opportunity

The HMS Alumni Council is seeking your help in recruiting prospective students and mentoring current students and recent graduates, with a particular focus on working with those underrepresented in medicine. In partnership with the School's Office of Recruitment and Multicultural Affairs and the Office of Alumni Affairs and Development, the Council hopes to infuse our alumni community's unique voices and experiences into its programs. To identify ways you can help, visit **alumni.hms.harvard.edu/survey.**

Distinguished Service Award for Harvard Medical School Alumni

Congratulations to DeWayne Pursley, MD '83 (Class of 1982). Pursley, the chief of neonatology at Beth Israel Deaconess Medical Center, and the 2022 winner of the Distinguished Service Award for Harvard Medical School Alumni. Pursley is being recognized for his invaluable efforts as a student mentor, an advocate for those seeking financial aid, and a leader in advancing the School's diversity and inclusion efforts. He was a member of his twenty-fifth and fortieth reunion committees and is a former member of the HMS Alumni Council. Learn more or nominate an alumna or alumnus at **alumni.hms.harvard.edu/service-award.**

Harvard Alumni Association Award

Harold "Hal" Burstein, MD '94 PhD '94, an HMS professor of medicine at Dana-Farber Cancer Institute, received a 2021 Harvard Alumni Association award for his outstanding service to Harvard University. At HMS, his leadership and engagement activities include serving as chair of an admissions subcommittee and serving as co-chair of his class's reunion committee. While a member of the HMS Alumni Council, Burstein also helped create the Distinguished Service Award for HMS Alumni.

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RANDY GLASS

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Heightened Concerns

Climate-driven changes in temperature, weather events, and human migration are among the factors that are altering the areas in which infectious-disease vectors such as mosquitoes, snails, and ticks can thrive. New or expanded habitats for these vectors can bring them and the diseases they carry into contact with unsuspecting—and unprotected—populations.